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Title

Angiogenesis affecting polypeptides, proteins, and compositions, and methods of use thereof.

Field of the Invention

The invention relates to polypeptides and proteins encoded thereby which are involved in vasculogenesis and/or angiogenesis. These agents may be targeted when producing materials and methods used in the diagnosis and therapy of angiogenesis-related conditions. The invention further relates to such diagnostic and therapeutic methods and agents.

Background of the Invention

Both vasculogenesis, the development of an interactive vascular system comprising arteries and veins, and angiogenesis, the generation of new blood vessels, play a role in embryonic development. In contrast, angiogenesis is limited in a normal adult to the placenta, ovary, endometrium, and sites of wound healing. Angiogenesis, or its absence, plays an important role in the maintenance of a variety of pathological states. Some of these states are characterized by neovascularization, e.g., cancer, diabetic retinopathy, glaucoma, and age related macular degeneration. Others, e.g., stroke, infertility, heart disease, ulcers, and scleroderma, are diseases of angiogenic insufficiency.

Angiogenesis has a number of stages (see, e.g., Zhu and Witte, Invest New Drugs 17:195-212, 1999). The early stages of angiogenesis include endothelial cell protease production, migration of cells, and proliferation. The early stages also appear to require some growth factors, with VEGF, TGF-A and selected chemokines all putatively playing a role. Later stages of angiogenesis include population of the vessels with mural cells (pericytes or smooth muscle cells), basement membrane production, and the induction of vessel bed specializations. The final stages of vessel formation include what is known as remodelling wherein a forming vasculature becomes a stable, mature vessel bed. Thus, the process is highly dynamic, often requiring coordinated spatial and temporal waves of gene expression.

The complex angiogenesis process is subject to disruption through interference with one or more critical steps, and numerous disease states can result from or be exacerbated by the disruption. Unregulated angiogenesis can cause or worsen disease, for example, ocular neovascularization has been implicated as the most common cause of blindness and underlies the pathology of approximately 20 eye diseases. In certain previously existing conditions such as arthritis, newly formed capillary blood vessels invade the joints and destroy cartilage. In diabetes, new capillaries formed in the retina invade the vitreous humour, causing bleeding and blindness.

In addition to pathologies linked to unregulated angiogenesis, insufficient angiogenesis can also lead to undesirable results. Dead or damaged tissue can lead to numerous pathologies, revascularization of damaged tissues through a healthy, normal angiogenic process is essential to preventing further complications.

Therefore, new targets and treatments that inhibit or enhance angiogenesis are needed. Identification of more key factors involved in any stage of angiogenesis could lead to new diagnostic methods for pathologic conditions related to angiogenesis. Further, elucidation and understanding of the key factors involved in angiogenesis could form the basis for new methods to investigate potential therapies for angiogenesis-related conditions.

Brief Summary of the Invention

In accordance with the objects outlined above, the present invention discloses eleven nucleic acid sequences and associated proteins which have key roles in vasculogenesis and/or angiogenesis. One object of the present invention is to present approaches for using the eleven novel factors as molecular targets for therapeutic intervention in angiogenesis-related disease states. It is a further object of the present invention to provide materials and methods that can be used to screen compounds for the ability to modulate angiogenesis or angiogenesis-related conditions.

Therapeutics specifically targeting the sequences and proteins identified herein are also provided as agents or compositions which modulate vasculogenesis or angiogenesis.

According to one embodiment of the invention, an isolated nucleic acid molecule according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 or a fragment or analogue thereof is provided which has the ability to stimulate or inhibit at least one biological activity selected from the group consisting of vasculogenesis, angiogenesis, vascular permeability, endothelial cell proliferation, endothelial cell differentiation, endothelial cell migration, and endothelial cell survival, or an isolated nucleic acid molecule which hybridizes to one of the foregoing sequences under stringent conditions The invention is also directed to isolated nucleic acid molecules which hybridizes to a compliment of a nucleic acid molecule described above, and an isolated siRNA molecule of at least 19 base pairs targeted to an isolated nucleic acid molecule described above.

According to a further embodiment of the invention, an expression vector comprising one of the novel nucleic acids is provided. The nucleic acid may be operatively associated with a regulatory nucleic acid controlling the expression of the polypeptide encoded by the nucleic acid.

The invention further comprises host cells genetically engineered to contain a nucleic acid as described above, or transfected by an expression vector described above.

According to a further embodiment of the invention, a method of treating an angiogenesis-related condition in a cell, group of cells, or organism is provided, comprising administering an expression vector as described above to the cell, group of cells, or organism.

The invention further comprises antibodies with specific reactivity to the nucleic acid molecules described above. The antibodies may be polyclonal or monoclonal and may further comprise detectable labels, such as fluorescent labels.

According to a further embodiment of the invention, a transgenic, non-human animal is provided which has been genetically engineered to contain a transgene comprising a nucleic acid as described above, and animals which contain and express the transgene.

According to a further embodiment of the invention, a pharmaceutical composition is provided which comprises a nucleic acid sequence as described above. The compound may be administered to a cell, group of cells, or organism to affect vasculogenesis or angiogenesis. The effect may be to increase or decrease vasculogenesis or angiogenesis, and the method may be employed where the cells, group of cells, or organism has an angiogenesis-related disorder. Such angiogenesis-related disorders include cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis, and rheumatoid arthritis.

According to a further embodiment of the present invention, an isolated polypeptide comprising a sequence of amino acids substantially corresponding to the amino acid sequence in any one of SEQ ID NO:s 3, 5, 8, 10, 13, 15, 18, 20, 22, 25, 27, 30, 32, 35, 37, 40, 42, 45, 47, 50, 52, 55, and 57 or a fragment or analogue thereof is provided which has the ability to affect angiogenesis in a cell, a group of cells, or an organism.

The invention further comprises host cells genetically engineered to express a polypeptide as described above, as well as antibodies specifically reactive with the polypeptides. The antibody may be polyclonal or monoclonal, and may further comprise a detectable label such as fluorescence.

According to a further embodiment of the invention, a transgenic, non-human animal is provided which has been genetically engineered to contain a transgene comprising a nucleic acid which encodes a polypeptide as described above, and animals that contain and express the transgene.

The invention further provides pharmaceutical compositions comprising an isolated polypeptide as described above. The pharmaceutical composition may be administered to a cell, group of cells, or organism in order to affect vasculogenesis or angiogenesis therein. Vasculogenesis or angiogenesis may be increased or decreased. The cell, group of cells, or organism may have an angiogenesis-related disorder. Representative angiogenesis-related disorders are noted above.

According to a further embodiment of the invention, a method of detecting an angiogenesis-related transcript in a cell in a patient is provided, the method

comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56, wherein an angiogenesis-related transcript is detected where hybridization is detected. The polynucleotide may comprise a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56. The biological sample may be a tissue sample, or sample of isolated nucleic acids such as mRNA. According to this method, the nucleic acids may be amplified prior to contacting the biological sample with the polynucleotide. Further, the polynucleotide is immobilized on a solid surface.

According to a further embodiment of the present invention, a method of affecting at least one bioactivity selected from angiogenesis and vasculogenesis in a vertebrate organism is provided, where method comprises the step of administering an effective angiogenesis or vasculogenesis affecting amount of a nucleotide or polypeptide described herein to the organism. The organism may be mammal, such as mice, rats, rabbits, guinea pigs, cats, dogs, pigs, cows, monkeys, and humans. Vasculogenesis or angiogenesis may be enhanced, increased, inhibited, or decreased. This method may be used on organisms that have an angiogenesis-related disorder, such as those disorders described above.

According to a further embodiment of the invention, a transgenic increased angiogenesis laboratory animal is provided which comprises one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is upregulated. Transgenic decreased angiogenesis laboratory animals are also provided, which comprise one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is down regulated or absent.

The terms "angiogenesis-related condition" or "angiogenesis-related disease (state)" as used herein mean a condition which is marked by either an excess or a deficit of vessel development or which is improved by an increase or decrease in vessel development. Disorders associated with increased angiogenesis include, but are not limited to, cancer (including solid tumors, leukemias, and tumor metastases), benign tumors (including hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas), retinopathy, macular degeneration, and corneal ulceration. Pathological states linked to decreased angiogenesis or states which can improve with increased angiogenesis include, but are not limited to, ischemic heart disease, infertility, ulcers, scleradoma, (insufficient) wound healing, ischemia, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans (ASO), Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, and stroke. Other angiogenesis related diseases include, but are not limited to, diseases associated with rubeosis (neovascularization of the angle) and diseases caused by the abnormal proliferation of fibrovascular or fibrous tissue including all forms of proliferative vitreoretinopathy, whether or not associated with diabetes, diseases with symptoms of chronic inflammation, such as inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

A "host cell" is a naturally occurring cell or a transformed cell that contains an expression vector and supports the replication or expression of the expression vector. Host cells may be cultured cells, explants, cells in vivo, and the like. Host cells may be prokaryotic cells such as E. coli, or eukaryotic cells such as yeast, insect, amphibian, or mammalian cells such as CHO, HeLa, and the like (see, e.g., the American Type Culture Collection catalog or web site, www.atcc.org).

The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, gamma-carboxyglutamate, and O-phosphoserine. "Amino acid analogs" refers to compounds that have the same basic chemical structure as a naturally occurring amino acid. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

The term "conservative modifications" or "conservatively modified variants" as used herein applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual probe sequences.

As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention.

As used herein, "label" or "detectable moiety" refers to a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. Examples of such labels include ^{32}P, fluorescent dyes, electron-dense reagents, enzymes, biotin, digoxigenin, or haptens and proteins which can be made detectable, e.g., by incorporating a radiolabel into the peptide or used to detect antibodies specifically reactive with the peptide.

As used herein, "vector" or "expression vector" refers to a nucleic acid construct, generated recombinantly or synthetically, with a series of specified nucleic acid elements that permit transcription of a particular nucleic acid in a host cell. The expression vector can be part of a plasmid, virus, or nucleic acid fragment. Typically, the expression vector includes a nucleic acid to be transcribed operably linked to a promoter.

The phrase "stringent hybridization conditions" as used herein refers to conditions under which sequences will hybridize. Stringent conditions are sequence-dependent and will be different in different circumstances. Skilled workers have access to significant amounts of descriptive material detailing reaction conditions that are appropriate for a given sequence. One example is Innis et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, Inc. N.Y.).

As used herein, the terms "inhibitors," "activators," and "modulators" of angiogenic polynucleotide and polypeptide sequences and angiogeneic activity refer to inhibitory, activating, or modulating molecules. "Inhibitors" are compounds that, e.g., bind to, partially or totally block activity, decrease, prevent, delay activation, inactivate, desensitize, or down regulate the activity or expression of angiogenesis proteins, e.g., antagonists. "Activators" are compounds that increase, open, activate, facilitate, enhance activation, sensitize, agonize, or up regulate angiogenesis protein activity. Inhibitors, activators, or modulators include genetically modified versions of angiogenesis proteins, e.g., versions with altered activity, as well as naturally occurring and synthetic ligands, antagonists, agonists, antibodies, small chemical molecules and the like. Assays for inhibitors and activators include, e.g., expressing the angiogenic protein in vitro, in cells, or cell membranes, applying putative modulator compounds, and then determining the functional effects on activity, as described above.

Brief Description of the Figures

Figure 1 shows a ratio-ratio plot with the $\log_2$ expression ratio of genes in a cDNA library when compared to embryonic brain endothelial cell portion versus embryonic

brain left over portion and adult brain endothelial cell portion versus adult brain left over portion;
Figure 2 shows a ratio-intensity plot with average intensity versus $\log_2$ expression ratio of genes in a cDNA library when compared to embryonic brain, heart, and skin endothelial cell versus left over embryonic portions and all adult endothelial cells and left over portions;
Figure 3 schematically depicts microarray data for gene HUP8001J6;
Figure 4 shows a wild type zebrafish embryo at 28 hpf;
Figure 5 shows a HUP8001J6 morphant embryo at 28 hpf;
Figure 6 shows a wild type zebrafish embryo at 56 hpf;
Figure 7 shows a HUP8001J6 morphant embryo at 56 hpf;
Figure 8 shows a wild type zebrafish at 48-56 hpf;
Figure 9 shows a HUP8001J6 morphant embryo at 48-56 hpf;
Figure 10 schematically depicts microarray data for gene HUP8001K17;
Figure 11 shows a HUP8001K17 morphant embryo at 28 hpf;
Figure 12 shows a HUP8001K17 morphant embryo at 56 hpf;
Figure 13 shows a HUP8001K17 morphant embryo at 48-56 hpf;
Figure 14 schematically depicts microarray data for gene HUP8001K21;
Figure 15 shows a HUP8001K21 morphant embryo at 28 hpf;
Figure 16 shows a HUP8001K21 morphant embryo at 56 hpf;
Figure 17 shows a HUP8001K21 morphant embryo at 48-56 hpf;
Figure 18 schematically depicts microarray data for gene HUP8003D24;
Figure 19 shows a HUP8003D24 morphant embryo at 48-56 hpf;
Figure 20 schematically depicts microarray data for gene HUP8004N1;
Figure 21 shows a HUP8004N1 morphant embryo at 28 hpf;
Figure 22 shows a HUP8004N1 morphant embryo at 56 hpf;
Figure 23 shows a HUP8004N1 morphant embryo at 48-56 hpf;
Figure 24 schematically depicts microarray data for gene HUP8010A10;
Figure 25 shows a HUP8010A10 morphant embryo at 28 hpf;
Figure 26 shows a HUP8010A10 morphant embryo at 56 hpf;
Figure 27 shows a HUP8010A10 morphant embryo at 48-56 hpf;
Figure 28 schematically depicts microarray data for gene NOC8003L17;
Figure 29 shows a NOC8003L17 morphant embryo at 28 hpf;
Figure 30 shows a NOC8003L17 morphant embryo at 56 hpf;
Figure 31 shows a NOC8003L17 morphant embryo at 48-56 hpf;
Figure 32 schematically depicts microarray data for gene NOC8009C9;
Figure 33 shows a NOC8009C9 morphant embryo at 28 hpf;
Figure 34 shows a NOC8009C9 morphant embryo at 56 hpf;
Figure 35 shows a NOC8009C9 morphant embryo at 48-56 hpf;
Figure 36 schematically depicts microarray data for gene NOC8009G23;
Figure 37 shows a NOC8009G23 morphant embryo at 28 hpf;
Figure 38 shows a NOC8009G23 morphant embryo at 56 hpf;
Figure 39 shows a NOC8009G23 morphant embryo at 48-56 hpf;
Figure 40 schematically depicts microarray data for gene OJC8003C9;
Figure 41 shows a OJC8003C9 morphant embryo at 28 hpf;
Figure 42 shows a OJC8003C9 morphant embryo at 56 hpf;
Figure 43 shows a OJC8003C9 morphant embryo at 48-56 hpf;
Figure 44 schematically depicts microarray data for gene OJC8009J7;
Figure 45 shows a OJC8009J7 morphant embryo at 28 hpf;
Figure 46 shows a OJC8009J7 morphant embryo at 56 hpf; and

Figure 47 shows a OJC8009J7 morphant embryo at 48-56 hpf.

Detailed Description

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention. Materials, the synthesis of which are not specifically described, are either commercially available or can be prepared using methods well known to those of skill in the art. Except as otherwise noted, all amounts including quantities, percentages, portions, and proportions, are understood to be modified by the word "about", and amounts are not intended to indicate significant digits. Except as otherwise noted, the articles "a", "an", and "the" mean "one or more". All documents cited are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

Identification of Candidate Genes

A cDNA Library was prepared by collecting the mRNA from purely isolated adult and embryonic mice vascular fragments. The collected mRNA was used to develop cDNA libraries with a broad coverage of genes expressed in the vasculature. Because of the variety in mouse age, the vascular genes represented those active at different times and in different situations in the vasculature.

After creation of the cDNA library, microarrays were created by printing DNA from the cDNA library onto a solid support as known in the art. The microarrays were used to reveal the gene candidates through gene expression profiling. Select tissues from adult and E 18.5 embryonic mice were collected. Tissue selection was based on the amount and purity of RNA available for extraction. After tissues were removed, they were separated into two portions using antibodies or lectins. The first portion, the endothelial cell fraction or EC, contained endothelial cells as well as pericytes and vascular smooth muscle cells which are tightly associated with the vascular fragments. The second portion, also referred to as the left over portion or LO, were those cells remaining after the EC was isolated.

From adult mice, brain and heart tissues were used, both the EC and LO of each. From embryonic mice, brain, heart, and skin, both EC and LO of each, were utilized. The RNA from each fraction was extracted. A common reference RNA (Universal Mouse Reference RNA; Stratagene, Inc.) was employed at this stage for reference purposes. The isolated RNA and the reference RNA were reverse transcribed then amplified twice through two rounds of antisense RNA amplification. The isolated RNA was labelled with the fluorophore cyanine-3 and the reference RNA with cyanine-5.

After labelling, the RNA was assayed through hybridization with the microarrays described above. The hybridized microarrays were scanned and image analysis used to process the experimental data. Normalizing the data through a signal intensity-based normalization algorithm allowed for statistical evaluation of differentially

expressed genes. Genes exhibiting differential expression were selected for further analysis.

Selection of Genes with Differential Expression

Using data collected as described above, certain genes were designated as selectively expressed in blood vessels. This was based on comparisons between adult and embryonic EC and LO values. Figure 1 shows a ratio-ratio plot of the data values obtained through comparisons between embryonic brain EC and LO genes and between adult brain EC and LO genes. A comparison of total adult EC with total embryonic EC was also conducted, data not shown. Data points represented with 'DT1 candidates' or 'DT2 candidates' were generally upregulated (>0 $\log_2$ expression ratio).

Other genes were designated as selectively expressed during angiogenesis through a different comparison of data. The total embryonic EC portion (i.e., brain, heart, and skin EC portions) was compared to all remaining tissues, including the total embryonic LO portion and all adult RNA (EC and LO of both brain and heart). Figure 2 shows a ratio-intensity plot with the average intensity versus $\log_2$ expression ratio of all genes. The data points marked DT3 candidates and DT4 candidates are those genes shown to be up regulated through this selective analysis. A comparison was also undertaken to analyze all EC portions versus all LO portions, data not shown.

A total of eleven genes of interest were selected for further analysis. Specific expression data for each gene follows throughout and includes a graph showing that gene's expression profile. Tables are used to show the intensity of the microarray signal, the $\log_2$ expression ratio, p-value, and rank (rank given only for certain fields). The highest rank was awarded to the gene with the highest expression ratio value, the lowest rank was assigned to the gene with the lowest expression value, based on expression ratio values. P-values are given as a value from zero to one. Values close to one indicate a gene that is upregulated, whereas values close to zero indicate a statistically down regulated gene. A statistically significant p-value of 0.05 corresponds to a p-value of 0.05 or 0.95.

For graphs, tables, and text the abbreviation eec/r refers to embryonic EC portions versus all remaining portions, ec/lo refers to all EC portions versus all LO portions, abeclo refers to adult brain EC portion versus adult brain LO portion, abecebec refers to adult brain EC portion versus embryonic brain EC portion, aheclo refers to adult heart EC portion versus adult heart LO portion, ebeclo refers to embryonic brain EC portion versus embryonic brain LO portion, eheclo refers to embryonic heart EC portion versus embryonic heart LO portion, and eseclo refers to embryonic skin EC portion versus embryonic skin LO portion..

Evaluation of Selected Genes

Further analysis of selected genes was conducted through knockdown technology in zebrafish. The process involves the use of specific antisense oligonucleotides that block translation from targeted mRNA molecule(s). This allows for inhibition of the gene of interest and allows for a determination of gene function in the development and health of the zebrafish. Zebrafish share genes for vertebrate functions with mammalian vertebrates such as mice and humans. Studies have demonstrated that

organ and/or tissue development in zebrafish can reliably predict effects in humans (See, *inter alia*, Shin and Fishman, From zebrafish to humans: Modular medical models, Ann. Rev. Genomics and Human Genet. 2002: 3: 311-340; Clark *et al.*, An oligonucleotide fingerprint normalized and expressed sequence tag characterized zebrafish library, Genome Res 2001 Sep;11(9):1594-602. Because of their rapid external development, zebrafish embryo development can be easily monitored and analyzed. The presence of a yolk sac helps provide data from the development of a critically deficient embryo further than that possible with other research organisms, such as mice.

To prepare the embryos, the zebrafish homolog of the target gene was identified. Then, a specific morpholino phosphorodiamidate oligonucleotide was designed to match the AUG initiation codon or splice acceptor/donor site of the target gene. To create a stock solution of morpholino, pellets containing 100 nmoles of the phosphorodiamidate oligonucleotides were dissolved in 33.3 µl milli-Q water, giving a concentration of 25 mg/ml, and stored at -20°C. To create injection solution, 8 µl of the stock solution was added to 92 µl of sterile-filtered 1X Danieu buffer (58 mM NaCl, 0.7 mM KCl, 0.4 mM $MgSO_4$, 0.6 mM $Ca(NO_3)_2$, 5 mM HEPES, pH 7.6) supplemented with 15mM Tris-Cl, pH 8.0. The 2 mg/ml injection solution was also stored at -20°C.

During injection, the materials and embryos were maintained at approximately 28°C. Injection needles were calibrated so that injection times could optimally be within a range of 100-600 msec. Embryos from the one cell stage to the early eight cell stage were used. The morpholinos were microinjected into the yolk sac. Specific injection volumes, or effective dose of the morpholino, are described below. Typical initial doses included 3, 6, and 12 ng (1.5, 3, and 6 nl, respectively). Toxicity at the 3 nl dose resulted in subsequent doses of 0.5, 1, and 2 ng (1, 2, and 4 nl, respectively). Approximately 40 embryos were injected at each dose level, and approximately 40 embryos were retained as non-injected controls.

After the morpholinos were injected into fertilized egg cells, the embryos engineered to have a knockdown of the specific gene were allowed to develop (See Nasevicius and Ekker, Effective targeted gene 'knockdown' in zebrafish, Nature Genetics vol 26, October 2000.). The embryos were monitored throughout development, both by examining morphology and undertaking specific analysis and assays of developing tissues.

In addition to single morpholino injections, double morpholino injections were performed as well. Specific injection volumes for double injections are described below. At the end of the first post-injection day, with embryos at the blastula or gastrula stage, propyl thioracil (PTU) 2x solution was added to the embryos, doubling their suspension volume. 48 hours post fertilization (hpf) the double injected embryos were fixed with cadherin 5 (cdh5) for *in situ* hybridization.

When 20% or more of the double injected embryos displayed low effect defects in the vasculature observed with cdh5, or when 10% or more of the embryos displayed medium or high effect defects, then microangiopathy and in situ hybridization with fli-1, flk-1, flt-4, tie-1, tie-2, and cdh5 were conducted. At least 120 embryos were administered the double morpholino dose, of which at least 100 were harvested at 24

hpf for *in situ* hybridization with the above-noted molecular markers. Remaining embryos were used for microangiopathy.

Data specific to the evaluation of each of the eleven targets are described below. In general, the morphology observations conducted at 24-28 hpf included an indication of whether the embryos exhibited general delay relative to control embryos. Further, cell death type and degree were recorded, general embryo shape and brain morphology were recorded as well. Finally, yolk sac edema, if present, was evaluated and recorded, as was heart morphology.

Also, at approximately 24 hpf, double morpholino embryos were evaluated for *in situ* hybridization of fli-1, flk-1, flt-4, tie-1, tie-2, and cdh5. Overall morphology and the degree of reduction of staining in the intersegmental vessels as compared to control embryos, correlating to a percentage of lost expression, were noted. Those embryos showing a loss of 1-35% of intersegmental expression were considered to have a low effect, those embryos showing a loss of 36-70% of intersegmental expression were considered to have a medium effect, and those embryos showing a loss of 71-100% of intersegmental expression were considered to have a high effect.

At 48-56 hpf various parameters were reviewed and recorded, such as general embryo shape, degree of cell death, blood circulation, and heart morphology. For the embryos fixed with cdh5, staining was evaluated throughout the vasculature as described immediately above.

Microangiopathy was also evaluated at 48hpf in double morpholino embryos. In order to observe the blood vessels, the embryos were transferred into a tricaine solution and the sinus venosa/common cardinal vein was injected with 10 µl FITC-Dextran solution (2,000,000 Da, 20 mg/ml).

Gene HUP8001J6

The gene having the sequence shown in SEQ ID NO:1 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 3. Specific data are given below in Table 1. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:2) and the human homolog (SEQ ID NO:4) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 3 and 5, respectively.

	intensity	log2 exp ratio	p-value	rank
eec/r	8,2	0,88		600
ec/lo	8,1	0,80		449
abec/o	7,6	0,60	1,00	
abecebec	8,3	0,27	0,76	
ahec/o	7,3	1,17	1,00	
ebec/o	9,1	-0,29	0,23	
ehec/o	8,1	1,21	1,00	
esec/o	8,1	-0,13	0,25	

Table 1: Expression profile data for gene HUP8001J6.

Based on this expression profile, the gene was further analyzed in zebrafish embryos. Two corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz265 and sz266, each targeted to one of the zebrafish genes. Six (6) ng of sz265 morpholino and 2 ng of sz266 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe *fli-1* revealed that 13% of the 16 morphant embryos assayed had high effects, that is, loss of 71-100% of intersegmental expression. The probe *flk-1*, VEGF receptor 2, indicated that 7% of the 15 morphants reviewed had high effects. When analyzed through the probe *tie-1*, all 15 morphants observed were normal. The probe *cdh5*, VE cadherin, indicated that all 23 morphants observed were normal. The probe *flt-4*, VEGF receptor 3, indicated that all 15 morphants observed were normal. And the probe *tie-2* showed all 15 observed morphants as normal.

The following table, Table 2, summarizes this data.

Probe	Number analyzed	Results
fli-1	16	13%H
flk-1	15	7%H
tie-1	15	normal
cdh5	23	normal
flt-4	15	normal
tie-2	15	normal

Table 2: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Both the wild type embryos, used as control, and the morphant embryos observed showed normal morphology. Figures 4 and 5 show the wild type and morphant embryos at 28 hpf, respectively. At 56 hpf the embryos were again observed, a wild type embryo is shown in Figure 6 and a morphant embryo in Figure 7. As highlighted by an arrow in the representative embryo of Figure 7, 82% of the 56 morphant embryos showed severe yolk sac edema. Further, 70% showed severely reduced blood flow and 14% showed reduced intersegmental blood flow.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 22 morphants revealed that 18% had reduced intersegmental expression, at a low effect level, whereas the remaining 82% were normal. Microangiography on 22 morphants was used to locate the presence of FITC-Dextran in various regions of the embryo. No FITC-Dextran was observed in the heart, head, nor was there any leaky vasculature. 14% of the morphants showed high effects of reduced intersegmental vasculature, and another 14% showed low effects of the same. Thus, 28% were affected by some changes to the intersegmental vasculature and 72% appeared normal. A wild type embryo at this time stage is shown in Figure 8, whereas Figure 9 shows a representative of the 48-56 hpf embryos analyzed. The arrow points to an area of reduced intersegmental vasculature.

Gene HUP8001K17

The gene having the sequence shown in SEQ ID NO:6 was identified as selectively expressed in blood vessels based on microarray data, see Figure 10. Specific data are given below in Table 3. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:7) and the human homolog (SEQ ID NO:9) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 8 and 10, respectively.

	intensity	log2 exp ratio	p-value	rank
eecfc	7,8	-0,11		6732
ecflo	7,8	0,59		804
abeclo	7,9	3,52	1,00	
abecabec	8,4	2,10	1,00	
ahecfo	7,5	-1,05	0,00	
ebeclo	8,8	2,15	1,00	
ahecfo	7,5	-0,07	0,42	
Ebeclo	7,5	-0,56	0,01	

Table 3: Expression profile data for gene HUP8001K17.

Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two different morpholinos were prepared, sz143 and sz144, each targeted to the zebrafish gene. Different amounts of morpholinos were administered as described below. The predetermined amount of each morpholino was administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf secondary *in situ* hybridization screens with six different probes were conducted.

One screen was performed on embryos that received 1 ng of sz143 morpholino and 4 ng of sz144 morpholino. Four probes specifically selected to analyze axial and intersegmental vessel expression revealed the following: using the *fli-1* probe, 6% of the 17 embryos analyzed had medium intersegmental expression effects. Another 18% had high effects. The probe *flk-1*, VEGF receptor 2, indicated that 20% of the 15 morphants reviewed had medium and 13% had high effects. When analyzed through the probe *tie-1*, 63% of the 16 morphants observed had high effects. The probe *cdh5*, VE cadherin, indicated that 4% of the 24 morphants observed had medium effects, and another 4% had high effects. The probe *flt-4*, VEGF receptor 3, indicated that all 14 morphants observed were normal, and the probe *tie-2* showed all 18 observed morphants as normal.

The other screen was performed on embryos that received 1.5 ng of sz143 morpholino and 6 ng of sz144 morpholino. The probe *fli-1* indicated that 42% of the 12 morphants analyzed had high effects. The *flk-1* probe demonstrated that 23%of the 13 morphants observed had high effects. The *tie-1* probe revealed 54% of 13 morphants had high effects. The probe *cdh5* indicated that 15% of 27 morphants had medium effects and another 11% had high effects. The probe *flt-4* indicated that all 14 morphants observed were normal. And the probe *tie-2*, showed all 18 observed morphants as normal.

The following Table 4 summarizes the foregoing data.

	Morphants with 1 ng sz143, 4 ng sz144		Morphants with 1.5 ng sz143, 6 ng sz144	
Probe	Number analyzed	Results	Number analyzed	Results
fli-1	17	6%M, 18%H	12	42%H
flk-1	15	20%M, 13%H	13	23%H
tie-1	16	63%H	13	54%H
cdh5	24	4%M, 4%H	27	15%M, 11%H
flt-4	13	normal	14	normal
tie-2	19	normal	18	normal

Table 4: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. The wild type embryos, used as control, showed normal morphology as expected. As indicated previously, Figure 4 shows a wild type embryo at 28 hpf. The morphant embryos received a 1.5 ng dose of sz143 and a 6 ng dose of sz144, all did not exhibit normal morphology. A representative embryo is shown in Figure 11. Twenty embryos were observed, 50% of them showed a curly down body, indicated by the arrowhead in Figure 11, with yolk tube extension, indicated with a short arrow. Mild cell death was observed in 60% of the embryos, as shown by the long arrow in Figure 11. Finally, 50% of the embryos had yolk cell edema.

At 56 hpf embryos were again observed, for reference a wild type embryo is shown in Figure 6. A morphant at the corresponding stage is shown in Figure 12. Twenty (20) embryos were observed, 90% had a curly down body as shown by the long arrow in Figure 12, with reduced head as indicated by the short arrow. Pericardial edema, shown by the arrowhead, was observed in 90% of the embryos and reduced blood flow was also seen in 90% of the embryos.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 18 morphants which had received 1 ng sz143 and 3 ng sz144 revealed that 28% had reduced intersegmental expression, at a low effect level, with short and curly tails. The remaining 72% were normal. The same *in situ* hybridization screen was conducted using 11 morphants which had received 2 ng sz143 and 6 ng sz144. This revealed that 9% had reduced intersegmental expression, at a low effect level, with very short tails. The remaining 91% were normal.

Microangiography on 26 morphants which had received 1.5 ng of sz143 and 6 ng of sz144 was used to locate the presence of FITC-Dextran in various regions of the embryo. No FITC-Dextran was observed in the heart, but 31% of the embryos had FITC-Dextran in the head and heart. A total of 27% of the morphants had reduced intersegmental vasculature, and leaky vasculature was observed in 35% of the embryos. Only 42% of the embryos appeared normal. The combined percentages are greater than 100% since some embryos exhibited more than one non-normal feature. Figure 13 shows a representative of the 48-56 hpf embryos analyzed. The arrow points to an area of reduced intersegmental vasculature, and the arrowhead indicates a point of leaky vasculature. For reference, a wild type embryo at this time stage is shown in Figure 8. The experimental data reveal that the gene is expressed by scattered cells in many organs, but most clearly seen in the CNS.

Gene HUP8001K21

The gene having the sequence shown in SEQ ID NO:11 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 14. Specific data are given below in Table 5. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:12) and the human homolog (SEQ ID NO:14) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 13 and 15, respectively.

	intensity	log2 exp ratio	p-value	rank
eec/r	8,5	0,88		594
ec/lo	8,4	0,80		442
abeclo	8,5	0,71	1,00	
abeceblec	8,8	-0,02	0,48	
ahec/o	8,0	1,15	1,00	
ebec/o	9,5	-0,03	0,47	
ehec/o	8,3	0,72	0,98	
esec/o	8,3	0,49	0,99	

Table 5: Expression profile data for gene HUP8001K21.

Based on this expression profile, the gene was further analyzed in zebrafish embryos. Two corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz257 and sz258, each targeted to one of the zebrafish genes. Twelve (12) ng of sz257 morpholino and 12 ng of sz258 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe *fli-1* revealed that all of the 15 morphant embryos assayed were normal. The probe *flk-1* indicated that 13% of the 16 morphants reviewed had low effects and 6% had high effects. When analyzed through the probe *tie-1*, all 15 morphants observed were normal. The probe *cdh5* indicated that all 26 morphants observed were normal. The probe *flt-4* indicated that all 17 morphants observed were normal, the probe *tie-2* showed all 20 observed morphants as normal.

The following table, Table 6, summarizes this data.

Probe	Number analyzed	Results
fli-1	15	normal
flk-1	16	13%L, 6%H
tie-1	15	normal
cdh5	26	normal
flt-4	17	normal
tie-2	20	normal

Table 6: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 15 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, yolk sac edema was observed in 47% of the 55 morphants analyzed. At 56 hpf a total of 53 embryos were observed, a representative morphant embryo is shown in Figure 16. As highlighted by the long arrow, expanded hindbrain was found in 34% of embryos. Yolk sac edema, shown by a short arrow, was also observed in 58% of embryos. An arrowhead points out the location checked for pericardial edema; it was not observed.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 20 morphants showed all as normal. Microangiography on 31 morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 17. Of the 31 embryos, 19% had FITC-Dextran in the heart but none had it in the heart and the head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 17. High effects were observed in 19% of the embryos, medium effects in 13% and low

effects in 29%. No leaky vasculature was observed. Normal embryos accounted for 19% of the sample.

HUP8003D24

The gene having the sequence shown in SEQ ID NO:16 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 18. Specific data are given below in Table 7. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:17) and two human homologs (SEQ ID NO:s19 and 21) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 18, 20, and 22, respectively.

	intensity	log2 exp ratio	p-value	rank
eecr	9,1	0,48		2061
ecre	9,0	1,30		149
abecre	8,1	3,14	1,00	
abecebec	8,7	2,26	1,00	
ahecre	8,9	0,23	0,85	
ebecre	9,1	0,51	0,90	
ehecre	9,5	1,32	1,00	
esecre	9,0	1,84	1,00	

Table 7: Expression profile data for gene HUP8003D24

Based on this expression profile, the gene was further analyzed in zebrafish embryos. Three corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz185 and sz186, which were targeted to the three zebrafish genes. For the lower dose group, 3ng of sz185 morpholino and 6ng of sz186 morpholino were administered to each fertilized egg. For the double dose group, 6ng of sz185 morpholino and 12ng of sz186 morpholino were administered. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In the lower dose group, the probe *fli-1* revealed that 18% of the 11 morphant embryos assayed had medium effects, i.e., 36-70% loss of intersegmental expression, and 18% had high effects. The probe *flk-1* indicated that 36% of the 11 morphants reviewed had high effects. The probe *tie-1* indicated that 29% of the 14 morphants observed had high effects. The probe *cdh5* indicated 31% of the 16 morphants observed had high effects, and 31% had medium effects. The probe *flt-4* indicated that all 16 morphants observed were normal, and the probe *tie-2* indicated that all 15 morphants observed were normal.

In the higher dose group, the probe *fli-1* revealed that 33% of the 3 morphant embryos assayed had low effects and 33% had medium effects. The probe *flk-1* indicated that 100%, or both of the 2 morphants reviewed, had medium effects. The probe *cdh5* indicated 100%, all 7 of the morphants observed had high effects. The probe *flt-4* indicated that all 3 morphants observed were normal, and the probe *tie-2* indicated that all 7 morphants observed were normal.

The following Table 8 summarizes the foregoing data.

	Morphants with 3 ng sz185, 6 ng sz186		Morphants with 6 ng sz185, 12 ng sz186	
Probe	Number analyzed	Results	Number analyzed	Results
fli-1	11	18%M, 36%H	3	33%L, 33%M

flk-1	11	36%H	2	100%M
tie-1	14	29%H	n/a	no data
cdh5	16	31%M, 31%H	7	100%H
flt-4	16	normal	3	normal
tie-2	15	normal	7	normal

Table 8: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Cell death was observed in 70% of the 66 embryos observed. Yolk sac edema was observed in 29% of the morphants. At 56 hpf a total of 66 embryos were observed for phenotypic characteristics. Yolk sac edema was observed in 42% of embryos, 35% showed reduced IS blood flow and 26% showed reduced blood flow.

Additional analyses were conducted on 48-56 hpf morphant embryos.
A primary *in situ* hybridization screen with *cdh5* on 21 morphants receiving the lower doses noted above (3ng sz185, 6ng sz86) showed 52% as normal. Low effects of reduced intersegmental expression were seen in 43% of the embryos, and medium effects in 5%. Embryos receiving the double doses (6ng sz185, 12ng sz186), when viewed at the 48-56 hpf stage revealed 74% of the that the 23 embryos observed were normal. Low effects of reduced intersegmental expression were observed in 22% and medium effects in 4% of the embryos.

Microangiography on morphants given the lower dose of morpholinos (3ng sz185, 6ng sz186) was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 19. Of the 33 embryos, none had FITC-Dextran in the heart, or the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 19. High effects were observed in 6% of the embryos, medium effects in 15% and low effects in 36%. No leaky vasculature was observed. Normal embryos accounted for 43% of the sample.

The data reveal that the gene is expressed in many locations, such as vessels and epithelial structures in the kidneys as well as in large vessels, megakaryocytes, in heart valves and in the skin epithelium.

Gene HUP8004N1

The gene having the sequence shown in SEQ ID NO:23 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 20. Specific data are given below in Table 9. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:24) and the human homolog (SEQ ID NO:26) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 25 and 27, respectively.

	intensity	log2 exp ratio	p-value	rank
eecfr	9,0	1,12		262
ec/o	9,0	0,75		516
abecfc	8,0	0,44	0,79	
abecebec	8,6	-0,80	0,03	
ahecfc	9,0	-0,47	0,02	
ebecfc	8,8	1,68	1,00	
ehecfc	9,3	1,18	1,00	
esecfc	9,0	1,22	1,00	

Table 9: Expression profile data for gene HUP8004N1

Based on this expression profile, the gene was further analyzed in zebrafish embryos. Two corresponding zebrafish genes were identified for targeting. Two morpholinos were prepared, sz223 and sz224, each targeted to one of the zebrafish genes. Two dosing strategies were employed. The first dose group received 2ng of sz223 morpholino and 1ng of sz224 morpholino in each fertilized egg. The second dose group received 1ng of sz223 morpholino and 0.5ng of sz224 morpholino in each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression in embryos from the second dose group (1ng sz223, 0.5ng sz224) was analyzed in the assay and results differed somewhat based on the probe used. The probe *fli-1* revealed that 7% of the 15 morphant embryos assayed had low effects, and 7% had high effects. The probe *flk-1* indicated that 7% of the 14 morphants reviewed had high effects. The probe *tie-1* indicated that 7% of the 14 morphants observed had low effects, and 7% had high effects. The probe *cdh5* indicated that 8% of the 26 morphants observed had medium effects. The probe *flt-4* indicated that all 15 morphants observed were normal, and the probe *tie-2* indicated that all 15 morphants observed were normal.

The following table, Table 10, summarizes this data.

Probe	Number analyzed	Results
fli-1	15	7%L, 7%H
flk-1	14	7%H
tie-1	14	7%L, 7%H
cdh5	26	8%M
flt-4	15	normal
tie-2	15	normal

Table 10: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 21 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, yolk sac edema was observed in 56% of the 59 morphants studied. At 56 hpf a total of 20 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure22. As indicated by the arrow, pericardial edema was observed in 35% of embryos, 65% had a blood pool in the yolk, also indicated by the arrow, and 30% showed reduced IS blood flow.

Additional analyses were conducted on 48-56 hpf morphant embryos from the second dose group. A primary *in situ* hybridization screen with *cdh5* on 22 morphants showed all as normal. Microangiography on 30 second dose group morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 23. Of the 30 embryos, 13% had FITC-Dextran in the heart, and 3% in the heart and head. Reduced intersegmental vasculature was seen as indicated

by the arrow in Figure 23. High effects were observed in 7% of the embryos and low effects in 20%. No leaky vasculature was observed. Normal embryos accounted for 57% of the sample.

The data reveal that the gene is expressed in specific endothelium. In kidneys, it is expressed by certain vessels and some other epithelial structures. There is also some expression in the liver.

Gene HUP8010A10

The gene having the sequence shown in SEQ ID NO:28 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 24. Specific data are given below in Table 11. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:29) and the human homolog (SEQ ID NO:31) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 30 and 32, respectively.

	intensity	log2 exp ratio	p-value	rank
ecad	8,8	0,98		424
oc/lo	8,7	0,36		1747
abecdo	8,4	0,26	0,63	
abecebec	8,2	-2,20	0,00	
ahecdo	8,4	-0,06	0,38	
ebecdo	8,7	0,72	0,95	
ehecdo	9,4	0,14	0,67	
esecdo	8,9	-0,37	0,03	

Table 11: Expression profile data for gene HUP8010A10

Based on this expression profile, the gene was further analyzed in zebrafish embryos. A corresponding zebrafish genes was identified for targeting. Two morpholinos were prepared, sz267 and sz268, each targeted to one of the zebrafish genes. In a first dosage group, 4ng of sz267 morpholino and 2ng of sz268 morpholino were administered to each fertilized egg. In a second dosage group, 6ng of sz267 morpholino and 3ng of sz268 morpholino were administered. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In the first dose group (4ng sz267, 2ng sz268), the probe *fli-1* revealed that 13% of the 15 morphant embryos assayed had high effects. The probe *flk-1* indicated that 33% of the 15 morphants reviewed had low effects and 20% had high effects. The probe *tie-1* indicated that all 17 morphants observed were normal. The probe *cdh5* indicated that 8% of the 25 morphants observed had high effects. The probe *flt-4* indicated that all 13 morphants observed were normal, and the probe *tie-2* indicated that all 16 morphants observed were normal.

In the second dose group (6ng sz267, 3ng sz268), the probe *fli-1* revealed that 25% of the 16 morphant embryos assayed had low effects, and 19% had high effects. The probe *flk-1* indicated that 33% of the 6 morphants reviewed had low effects. The probe *tie-1* indicated that 67% of the 15 morphants observed had high effects. The probe *cdh5* indicated that 21% of the 24 morphants observed had low effects, 13% had medium effects, and 29% had high effects. The probe *flt-4* indicated that all 15 morphants observed were normal, and the probe *tie-2* indicated that all 15 morphants observed were normal.

The following Table 12 summarizes the foregoing data.

	Morphants with 4 ng sz267, 2 ng sz268		Morphants with 6 ng sz267, 3 ng sz268	
Probe	Number analyzed	Results	Number analyzed	Results
fli-1	15	13%H	16	25%L, 19%H
flk-1	15	33%L, 20%H	6	33%L
tie-1	17	normal	15	67%H
cdh5	25	8%H	24	21%L, 13%M, 29%H
flt-4	13	normal	15	normal
tie-2	16	normal	15	normal

Table 12: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 25 shows a representative morphant embryo at 28 hpf. Cell death in the head was observed in 47% of the 61 embryos observed, as indicated by the arrow in Figure 25. The arrowhead indicates expanded hindbrain, which was seen in 51% of embryos. Mild yolk sac edema was observed in 21% of the morphants. At 56 hpf a total of 59 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 26. The arrow indicates expanded hindbrain, which was seen in 44% of embryos. Mild yolk sac edema was observed in 29% of the morphants and is indicated by the arrowhead. Reduced IS blood flow was noted in 14% of the embryos, and reduced blood flow was found in 17% of the embryos.

Additional analyses were conducted on 48-56 hpf morphant embryos from the second dose group. A primary *in situ* hybridization screen with *cdh5* on 19 morphants showed 68% as normal. Low effects of reduced intersegmental expression were seen in 32% of the embryos. Microangiography on morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 27. Of the 32 embryos, none had FITC-Dextran in the heart, or the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 27. High effects were observed in 6% of the embryos, medium effects in 3% and low effects in 34%. No leaky vasculature was observed. Normal embryos accounted for 56% of the sample.

Gene NOC8003L17

The gene having the sequence shown in SEQ ID NO:33 was identified as selectively expressed in blood vessels based on microarray data, see Figure 28. Specific data are given below in Table 13. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:34) and the human homolog (SEQ ID NO:36) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 35 and 37, respectively.

	intensity	log2 exp ratio	p-value	rank
eec/r	7,7	-0,06		6087
ec/lo	7,6	0,40		1547
abec/o	7,5	1,47	0,97	
abecebec	8,3	0,30	0,77	
ahec/o	7,2	-0,04	0,41	
ebec/o	8,3	1,87	1,00	
ehec/o	7,8	0,60	0,99	
esec/o	7,5	-0,13	0,24	

Table 13: Expression profile data for gene NOC8003L17

Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz180 and sz181, each targeted to the zebrafish gene. In a first dose group, 12ng of sz180 and 1ng of sz181 were administered to each fertilized egg. In a second dose group, 12ng of sz180 and 2ng of sz181 were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression in embryos from the first dose group was analyzed in the assay and results differed somewhat based on the probe used. The probe *fli-1* revealed that 40 of the 15 morphant embryos assayed had high effects. The probe *flk-1* indicated that all 7 of the morphants reviewed were normal. The probe *tie-1* indicated that all 15 morphants observed were normal. The probe *cdh5* indicated that 15% of the 20 morphants observed had low effects, as well as 5% with medium effects and 30% with high effects. The probe *flt-4* indicated that all 11 morphants observed were normal, and the probe *tie-2* indicated that all 16 morphants observed were normal.

The following table, Table 14, summarizes this data.

Probe	Number analyzed	Results
fli-1	15	40%H
flk-1	7	normal
tie-1	15	normal
cdh5	20	15%L, 5%M, 30%H
flt-4	11	normal
tie-2	16	normal

Table 14: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 29 shows a representative morphant embryo. As indicated by the arrow, yolk sac edema was observed in 67% of the 48 morphants studied. Embryos observed at 56 hpf demonstrated normal morphology, a representative embryo is shown in Figure 30.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 14 morphants from the second dose group showed 79% as normal, the remaining 29% showing medium effects of reduced intersegmental expression. Microangiography on 29 first dose group morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 31. Of the 29 embryos, none had FITC-Dextran in the heart, 3% had FITC-Dextran in the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrow in Figure 31. High effects were observed in 7% of the embryos, medium effects in 3% and low effects in 38%. No leaky vasculature was observed. Normal embryos accounted for 45% of the sample.

GeneNOC8009C9

The gene having the sequence shown in SEQ ID NO:38 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 32. Specific data are given below in Table 15. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:39) and the human homolog (SEQ ID NO:41) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 40 and 42, respectively.

	intensity	log2 exp ratio	p-value	rank
eedr	8,1	0,84		685
eclo	8,0	1,19		184
abeclo	7,4	1,57	1,00	
abeceb ec	8,1	1,44	1,00	
ahecl o	8,4	0,12	0,74	
ebeclo	8,0	1,52	1,00	
ehecl o	8,3	0,53	0,98	
esecl o	7,9	2,41	1,00	

Table 15: Expression profile data for gene NOC8009C9

Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish genes was identified for targeting. Two morpholinos were prepared, sz241 and sz242, targeted to the zebrafish gene. Three (3)ng of sz241 morpholino and 1ng of sz242 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe *fli-1* revealed that 7% of the 15 morphant embryos assayed had medium effects. The probe *flk-1* indicated that all 15 morphants observed were normal. The probe *tie-1* indicated that 7% of the 15 morphants observed had high effects. The probe *cdh5* indicated that 15% of the 20 morphants observed had low effects. Medium effects were seen in 5% and high effects in 15%. The probe *flt-4* indicated that all 15 morphants observed were normal, and the probe *tie-2* indicated that all 16 morphants observed were normal.

The following table, Table 16, summarizes this data.

Probe	Number analyzed	Results
fli-1	15	7%M
flk-1	15	normal
tie-1	15	7%H
cdh5	20	15%L, 5%M, 15%H
flt-4	15	normal
tie-2	16	normal

Table 16: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 33 shows a representative morphant embryo at 28 hpf. Mild cell death was observed in 25% of the 53 embryos observed. At 56 hpf 52 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 34. As indicated by the arrow, pericardial edema was seen in 13% of embryos. The arrowhead points toward a region of yolk sac edema, seen in 25% of embryos.

Reduced IS blood flow was observed in 13% and 15% showed reduced axial blood flow.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 31 morphants showed all as normal. Microangiography on morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 35. Of the 29 embryos, 7% had FITC-Dextran in the heart, and 14% in the heart and head. Reduced intersegmental vasculature was seen as indicated by the arrows in Figure 35. High effects were observed in 3% of the embryos, medium effects in 3% and low effects in 21%. No leaky vasculature was observed. Normal embryos accounted for 52% of the sample. The data reveal that the gene is expressed in and around the heart and around organs, including some expression in select organs.

Gene NOC8009G23

The gene having the sequence shown in SEQ ID NO:43 was identified as selectively expressed during angiogenesis based on microarray data, see Figure 36. Specific data are given below in Table 17. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:44) and the human homolog (SEQ ID NO:46) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 45 and 47, respectively.

	intensity	log2 exp ratio	p-value	rank
eec/i	8,3	0,23		3262
ec/lo	8,2	1,19		185
abeclo	7,2	2,94	1,00	
abecebec	8,1	2,09	1,00	
ahaclo	8,0	1,15	1,00	
ebaclo	8,2	0,75	0,94	
ehaclo	9,0	-0,02	0,47	
eseclo	8,1	2,51	1,00	

Table 17: Expression profile data for gene NOC8009G23

Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz149 and sz150, each targeted to the zebrafish gene. In a first dose group, 1.5ng of sz149 morpholino and 1.5ng of sz150 morpholino were administered to fertilized eggs. In a second dose group, 2ng of sz149 morpholino and 2ng of sz150 morpholino were administered to fertilized eggs. In a third dose group, 3ng of sz149 morpholino and 3ng of sz150 morpholino were administered to fertilized eggs. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In studies with embryos from the second dose group, the probe *fli-1* revealed that 21% of the 14 morphant embryos assayed had high effects. The probe *flk-1* indicated that all 16 morphants reviewed were normal. The probe *tie-1* indicated that 36% of the 22 morphants observed had high effects. The probe *cdh5* indicated that 13% of the 15 morphants observed had low effects with breaks in axial expression. The probe *flt-4* indicated that all 16 morphants observed were normal, and the probe *tie-2* indicated that all 13 morphants observed were normal.

In studies from the second dose group, the probe *fli-1* revealed that 13% of the 15 morphant embryos assayed had medium effects, 27% had high effects. The probe

flk-1 indicated that 7% of the 15 morphants reviewed had low effects, 7% had medium effects and 20% had high effects. The probe *tie-1* indicated that 62% of the 13 morphants observed had high effects. The probe *cdh5* indicated that 25% of the 12 morphants observed had high effects, some with breaks in axial expression. The probe *flt-4* indicated that 13% of the 15 morphants observed had low effects in the axial vessels, including breaks in axial expression and severely malformed tails. The probe *tie-2* indicated that all 8 morphants observed were normal.

The following Table 18 summarizes the foregoing data.

	Morphants with 2 ng sz149, 2 ng sz150		Morphants with 3 ng sz149, 3 ng sz150	
Probe	Number analyzed	Results	Number analyzed	Results
fli-1	14	21%H	15	13%M, 27%H
flk-1	16	normal	15	7%L, 7%M, 20%H
tie-1	22	36%H	13	62%H
cdh5	15	13%L***	12	25%H***
flt-4	16	normal	15	13% low axial effects
tie-2	13	normal	8	normal

Table 18: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 37 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, cell death was observed in 40% of the 20 embryos observed. As indicated by the arrowhead, yolk sac edema was observed in 55% of the morphants. Curly down body was seen in 40% of morphants. At 56 hpf a total of 20 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure38. As shown by the arrow, pericardial edema was observed in 55% of morphants. The arrowhead points toward yolk sac edema, observed in 55% of morphants. Curly down body was reported in 30% of embryos.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 22 morphants from the first dose group showed 90% as normal. Low effects of reduced intersegmental expression and curly down embryos were seen in 5% of the embryos, and high effects with very short tails were seen in 5% of embryos. A primary *in situ* hybridization screen with *cdh5* was also performed on 20 morphants from the third dose group, showing 80% as normal. Low effects of reduced intersegmental expression were seen in 5% of the embryos, and medium effects in 15% of embryos.

Microangiography on morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 39. Of the 25 embryos, none had FITC-Dextran in the heart, or the heart and head. Reduced intersegmental vasculature was seen in 24% of the embryos as indicated by the arrow in Figure 39. No leaky vasculature was observed. Normal embryos accounted for 76% of the sample, in example of normal intersegmental vessels is indicated by the arrowhead.

Gene OJC8003C9

The gene having the sequence shown in SEQ ID NO:48 was identified as selectively expressed in blood vessels based on microarray data, see Figure 40. Specific data are given below in Table 19. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:49) and the human homolog (SEQ ID NO:51) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 50 and 52, respectively.

	intensity	log2 exp ratio	p-value	rank
eec/r	8,1	0,67		1246
ec/lo	8,0	1,37		123
abec/o	7,1	2,90	1,00	
abecebec	8,1	0,59	0,92	
ahec/o	7,6	0,19	0,85	
ebec/o	8,7	1,41	1,00	
ehec/o	8,4	1,89	1,00	
esec/o	7,7	1,28	1,00	

Table 19: Expression profile data for gene OJC8003C9

Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz129 and sz130, each targeted to the zebrafish gene. In a first dose group, 3ng of sz129 morpholino and 4.5ng of sz130 morpholino were administered to each fertilized egg. In a second dose group, 4ng of sz129 morpholino and 6ng of sz130 morpholino were administered to each fertilized egg. In a third dose group, 6ng of sz129 morpholino and 8ng of sz130 morpholino were administered to each fertilized egg. In a fourth dose group, 6ng of sz129 morpholino and 9ng of sz130 morpholino were administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. In embryos from the second dose group, the probe *fli-1* revealed that 20% of the 10 morphant embryos assayed had low effects, 10% had medium effects and 10% had high effects. The probe *flk-1* indicated that 11% of the 9 morphants reviewed had low effects, 33% had medium effects and 11% had high effects. The probe *tie-1* indicated that 22% of the 9 morphants observed had high effects. The probe *cdh5* indicated that 14% of the 7 morphants observed had medium effects and 14% had high effects. The probe *flt-4* indicated that all 9 morphants observed were normal, and the probe *tie-2* indicated that all 7 morphants observed were normal.

In embryos from the third dose group, the probe *fli-1* revealed that 10% of the 10 morphant embryos assayed had medium effects, and 50% had high effects. The probe *flk-1* indicated that 25% of the 12 morphants reviewed had medium effects and 25% had high effects. The probe *tie-1* indicated that 17% of the 6 morphants observed had low effects, and 50% had high effects. The probe *cdh5* indicated that 40% of 5 morphants observed had medium effects. The probe *flt-4* indicated that all 9 morphants observed were normal, and the probe *tie-2* indicated that all 6morphants observed were normal.

The following Table 20 summarizes the foregoing data.

	Morphants with 3 ng sz185, 6 ng sz186		Morphants with 6 ng sz185, 12 ng sz186	
Probe	Number	Results	Number	Results

	analyzed		analyzed	
fli-1	10	20%L, 10%M, 10%H	10	10%M, 50%H
flk-1	9	11%L, 33%M, 11%H	12	25%M, 25%H
tie-1	9	22%H	6	17%L, 50%H
cdh5	7	14%M, 14%H	5	40%M
flt-4	9	normal	9	normal
tie-2	7	normal	6	normal

Table 20: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 41 shows a representative morphant embryo at 28 hpf. As indicated by the arrow, curly down body was found in 35% of the 20 morphants observed. At 56 hpf a total of 20 embryos were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 42. As indicated by the long arrow, 60% of the embryos had cell death with an associated expanded hindbrain ventricle. Yolk sac edema was observed in 25% of embryos, as indicated by the short arrow. The arrowhead points out the lack of pericardial edema associated with the yolk sac edema.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 19 morphants from the first dose group showed all were normal. The primary *in situ* hybridization screen with *cdh5* on 10 morphants from the fourth dose group showed only 90% normal, the remaining 10% exhibiting low effects with curly tails. Microangiography on 19 morphants from the third dose group was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 43. Of the 19 embryos, none had FITC-Dextran in the heart and head but 16% had it in the heart alone. Reduced intersegmental vasculature was seen in 37% of the embryos. No leaky vasculature was observed. Normal embryos accounted for 47% of the sample.

Gene OJC8009J7

The gene having the sequence shown in SEQ ID NO:53 was identified as selectively expressed in blood vessels based on microarray data, see Figure 44. Specific data are given below in Table 21. Using sequence and annotation databases the equivalent gene in mice (SEQ ID NO:54) and the human homolog (SEQ ID NO:56) was also deduced. Proteins encoded by these sequences are given at SEQ ID NO:s 55 and 57, respectively.

	intensity	log2 exp ratio	p-value	rank
eec/r	8,5	0,62		1445
eo/o	8,3	1,03		257
abec/o	8,3	2,37	1,00	
abecebec	9,2	0,38	0,84	
ahec/o	7,9	0,93	1,00	
ebec/o	8,8	1,53	1,00	
ehec/o	8,8	1,03	1,00	
esec/o	8,5	0,48	0,99	

Table 21: Expression profile data for gene OJC8009J7

Based on this expression profile, the gene was further analyzed in zebrafish embryos. One corresponding zebrafish gene was identified for targeting. Two morpholinos were prepared, sz175 and sz176, each targeted to the zebrafish gene. Two (2) ng of sz175 morpholino and 12ng of sz176 morpholino were

administered to each fertilized egg. The embryos were allowed to develop. At 24 hpf a secondary *in situ* hybridization screen with six different probes was conducted.

Intersegmental expression was analyzed in the assay and results differed somewhat based on the probe used. The probe *fli-1* revealed that 7% of the 14 morphant embryos assayed had low effects, and 29% had high effects. The probe *flk-1* indicated that 25% of the 12 morphants reviewed had low effects and 8% had high effects. The probe *tie-1* indicated that 11% of the 9 morphants observed had medium effects and 11% had high effects. The probe *cdh5* indicated that 19% of the 16 morphants observed had low effects, 6% had medium effects, and 19% had high effects. The probe *flt-4* indicated that all 10 morphants observed were normal, and the probe *tie-2* indicated that all 6 morphants observed were normal.

The following table, Table 22, summarizes this data.

Probe	Number analyzed	Results
fli-1	14	7%L, 29%M
flk-1	12	25%L, 8%H
tie-1	9	11%M, 11%H
cdh5	16	19%L, 6%M, 19%H
flt-4	10	normal
tie-2	6	normal

Table 22: secondary *in situ* hybridization data

At 28 hpf embryos were observed morphologically. Figure 45 shows a representative morphant embryo at 28 hpf. As evidenced from the figure, particularly when viewed in light of the 28 hpf wild type embryo of Figure 4, the morphants exhibited normal morphology. At 56 hpf embryos again were observed for phenotypic characteristics, a representative morphant embryo is shown in Figure 46. Again, the normal morphology observed in the embryos can be easily understood when Figure 46 is viewed in light of the 56 hpf wild type embryo of Figure 6.

Additional analyses were conducted on 48-56 hpf morphant embryos. A primary *in situ* hybridization screen with *cdh5* on 17 morphants showed 88% as normal. Medium effects of reduced intersegmental expression were seen in the other 12% of embryos. Microangiography on morphants was used to locate the presence of FITC-Dextran in various regions of the embryo, see Figure 47. Of the 33 embryos, none had FITC-Dextran in the heart and head combined, but 4% had it in the heart alone. Reduced intersegmental vasculature was seen in 15% of embryos. No leaky vasculature was observed. Normal embryos accounted for 81% of the sample. The leaks observed came from blood vessels in the posterior head as indicated by the arrowhead.

Novel Applications Ascertained from *in vivo* Data

The present invention relates to the eleven gene targets, and proteins related thereto, which were originally identified as upregulated during vasculogenesis or angiogenesis through microarray evaluation and subsequently proven to play a critical role *in vivo* with zebrafish embryo experimentation. These genes and proteins can form the basis of novel methods and treatments directed to

angiogenesis-related conditions. For example, biological samples from a patient suspected of suffering from an angiogenesis-related condition can be screened to ascertain if genes or proteins of the present invention are expressed at the correct time, location, and intensity in the patient. Such screening methods form part of the claimed invention. If a gene and/or protein is identified as improperly expressed, therapies to correct the condition such as gene therapy or medicament can be initiated according to methods and procedures described herein or known in the art. With such specific data as is now possible using tools described herein, rapid diagnosis and specific, targeted treatment is possible.

One type of screening method envisioned relies on gene amplification for detecting patients with conditions related to vasculogenesis or angiogenesis. Such methods could employ PCR, in situ hybridisation, and/or Southern blotting techniques to elucidate the condition. Another type of screening method could be based on evaluations of gene expression, using known techniques such as quantitative PCR, microarrays, Northern blotting, or in situ hybridisation. Yet another type of screening method that could be used would measure or monitor protein expression and could be effected with techniques such as immunohistochemistry, Western blotting, ELISA, or FACS.

If it is determined, through methods of the present invention or other methods, that an angiogenesis-related condition could be improved through administration of compounds containing genes and/or proteins according to the invention, one or more of the genes and/or proteins could be administered together or sequentially by methods known in the art.

Isolated nucleic acid molecules or proteins of the present invention can be obtained, for example, by synthesis using standard direct peptide synthesizing techniques or recombinant methods. Proteins may be isolated or purified in a variety of ways known to those skilled in the art, such as electrophoretic purification or chromatographic techniques.

Administration of the compounds of the present invention can be effected by any method that enables delivery of the compounds to the site of desired action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), and topical administration.

Gene therapy approaches may be used to introduce nucleotides of the present invention into a cell, group of cells, or organism. Both *in vivo* and *ex vivo* methods can be utilized. Vectors typically are used in this procedure. Non-virus or virus vectors could be employed, for example recombinant adenovirus or retrovirus. According to this use, the desired gene is introduced into a DNA virus or RNA virus, such as avirulent retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, poxvirus, poliovirus, Sindbis virus, Sendai virus, SV40, and immunodeficiency virus (HIV). The recombinant virus is then infected into the target cell(s). Multiple genes could be incorporated in a single vector, alternatively, they could be introduced to the target cell(s) in separate vectors simultaneously or sequentially. These methods are known in the art and are described in numerous patents and publications.

Another means to interfere with gene expression or protein production contemplated by the present invention is to employ small interfering RNA (siRNA). siRNA comprises a sense and antisense strand of RNA corresponding to the gene of interest, for example, SEQ ID NO:2. A siRNA molecule consists of approximately 19 nucleotides plus an overhang of approximately 2 nucleotides at the 3' end. Some preferred methods include between 19-23 nucleotides plus 3' overhang. The siRNA is introduced to the cell or cells of interest through known methods. Following introduction, the cell or cells destroy ssRNA having the same sequence. This results in a reduction or prevention in translation of a targeted gene and a corresponding reduction or prevention in protein production.

The amount of active compound administered can be determined after assessing the subject being treated, the severity of the disorder or condition, the rate of administration, and the disposition of the compound. Doses may be administered all at once, or spread out over a discrete time period.

Compounds of the present invention may be applied as a sole therapy or may involve one or more other active medicinal or pharmaceutical agent. Compositions may include carriers, adjuvants, buffers, or excipients as known in the art. If desired, the compositions may further contain ingredients such as flavorings, sweeteners, binders, dyes, lubricating agents, perfume, thickening agents, stabilizers, emulsifiers, dispersants, suspending agents, preservatives, and pH regulating agents. Compositions may be in any suitable form, for example, tablet, capsule, pill, powder, sustained release formulation, solution, suspension, emulsion, ointment or cream. The compositions may be sterile. Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known or apparent to those skilled in this art. The pharmaceutical compositions of the present invention that have been described can be applied to all diseases that require vasculogenic or angiogenic therapy.

For example, one method for the treatment of an angiogenesis-related disorder involves a composition according to the present invention used to vascularize ischemic tissue. There are many ways to determine if a tissue is at risk of suffering ischemic damage from undesirable vascular occlusion. Such methods are well known in the art and include, for example, imaging techniques such as MRI to evaluate myocardial disease. After determining where and when to apply compositions of the present invention, the compositions can be administered to increase angiogenesis in tissue affected by or at risk of being affected by a vascular occlusion. This could be an effective means of preventing and/or attenuating ischemia in such tissue. Methods are known in the art to evaluate and measure the degree to which ischemia has been attenuated.

Further treatment methods according to the present invention include the use of any known technique that permits visualization, measurement, and/or evaluation of the functionality and degree of ischemia of the patient's heart. Such evaluations could be made prior to initiating treatment, during the course of treatment, after treatment has been completed, or at some or all stages. Examples of such techniques include echocardiography, cardiovascular nuclear imaging, magnetic resonance imaging, and contrast angiography.

Although the present invention takes a step forward in the understanding of vasculogenesis and angiogenesis, and treatments for conditions related to the same, there is still a need in the art to further understand these conditions. Therefore, the present invention further contemplates the creation and use of non-human transgenic animals which could be used for analysis and experimentation. Transgenic animals containing mutant, knock-out or modified genes corresponding to those disclosed herein are therefore also included in the invention. Transgenic animals are genetically modified animals into which recombinant, exogenous or cloned genetic material has been experimentally transferred. Such genetic material is often referred to as a transgene. The nucleic acid sequence of the transgene may be integrated either at a locus of a genome where that particular nucleic acid sequence is not otherwise normally found or at the normal locus for the transgene. The transgene may consist of nucleic acid sequences derived from the genome of the same species or of a different species than the species of the target animal.

Transgenic animals can be produced by a variety of different methods including transfection, electroporation, microinjection, gene targeting in embryonic stem cells and recombinant viral and retroviral infection as known in the art. The method of introduction of nucleic acid fragments into recombination competent mammalian cells can be by any method that favors co-transformation of multiple nucleic acid molecules. Detailed procedures for producing transgenic animals are available to one skilled in the art, for example, U.S. Pat. Nos. 5,489,743 and 5,602,307.

Transgenic technology can be used to produce animals which lack one or more of the eleven genes described above. Such knockout animals can be used, especially when their growth and development is measured against data from a wild type or control animal, to elucidate timing and function of the deleted gene(s). Further, these animals could also be engineered to exhibit angiogenesis-related disease states, thus furthering the understanding of the role of the particular gene(s) in the progression of the selected disease. This knowledge would be an advance in the state of the art and could lead to promising new therapies for the prevention, management, and cure of disease.

Further uses of transgenic animals according to the present invention include replacement of one or more of the above-identified gene(s) in the research organism with the human homolog of the gene. For example, a transgenic mouse whose gene corresponding to SEQ ID NO:7 has been replaced with the human homolog, SEQ ID NO:9. While it is accepted that research into effective drug therapies can be conducted in animal models, such a transgenic mouse could be a more effective screening tool into potential drug candidates for human use.

We Claim:

1. An isolated nucleic acid molecule according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 or a fragment or analogue thereof which has the ability to stimulate or inhibit at least one biological activity selected from the group consisting of vasculogenesis, angiogenesis, vascular permeability, endothelial cell proliferation, endothelial cell differentiation, endothelial cell migration, and endothelial cell survival, or an isolated nucleic acid molecule which hybridizes to one of the foregoing sequences under stringent conditions.

2. An isolated nucleic acid molecule which hybridizes to the compliment of a nucleic acid molecule according to Claim 1 under stringent conditions.

3. An isolated siRNA molecule targeted to an isolated nucleic acid molecule according to Claims 1 or 2, wherein the isolated siRNA molecule is at least 19 base pairs long.

4. An expression vector comprising the nucleic acid according to Claims 1 or 2, optionally the nucleic acid may be operatively associated with a regulatory nucleic acid controlling the expression of the polypeptide encoded by said nucleic acid.

5. A host cell genetically engineered to contain a nucleic acid according to Claims 1 or 2.

6. A host cell transfected with an expression vector according to Claim 4.

7. A method of treating an angiogenesis-related condition in a cell, group of cells, or organism, comprising the step of administering an expression vector according to Claim 4 to the cell, group of cells, or organism.

8. An antibody with specific reactivity to a nucleic acid according to Claims 1 or 2, wherein the antibody may preferably be polyclonal or monoclonal and wherein the antibody may further comprise a detectable label such as a fluorescent label.

9. A transgenic, non-human animal which has been genetically engineered to contain a transgene comprising a nucleic acid according to Claims 1 or 2, preferably, the transgene may be expressed.

10. A pharmaceutical composition comprising a nucleic acid sequence according to Claims 1 or 2.

11. A method of affecting vasculogenesis or angiogenesis in a cell, group of cells, or organism, comprising the step of administering a pharmaceutical composition according to Claim 16 to the cell, group of cells, or organism, the affecting may preferably cause an increase or decrease, more preferably, the cell, group of cells, or organism has an angiogenesis-related disorder such as cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis,

arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

12. An isolated polypeptide comprising a sequence of amino acids substantially corresponding to the amino acid sequence in any one of SEQ ID NO:s 3, 5, 8, 10, 13, 15, 18, 20, 22, 25, 27, 30, 32, 35, 37, 40, 42, 45, 47, 50, 52, 55, and 57 or a fragment or analogue thereof, said polypeptide having the ability to affect angiogenesis in a cell, a group of cells, or an organism.

13. A host cell genetically engineered to express a polypeptide according to Claim 12.

14. An antibody specifically reactive with a polypeptide according to Claim 12, wherein the antibody may preferably be polyclonal or monoclonal and wherein the antibody may further comprise a detectable label such as a fluorescent label.

15. A transgenic, non-human animal which has been genetically engineered to contain a transgene comprising a nucleic acid which encodes a polypeptide according to Claim 12, preferably, the transgene may be expressed.

16. A pharmaceutical composition comprising an isolated polypeptide according to Claim 12.

17. A method of affecting vasculogenesis or angiogenesis in a cell, group of cells, or organism, comprising the step of administering a pharmaceutical composition according to Claim 16 to the cell, group of cells, or organism, the affecting may preferably cause an increase or decrease, more preferably, the cell, group of cells, or organism has an angiogenesis-related disorder such as cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

18. A method of detecting an angiogenesis-related transcript in a cell in a patient, the method comprising contacting a biological sample from the patient with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56, wherein an angiogenesis-related transcript is detected where hybridization is detected, preferably the polynucleotide comprises a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56, preferably the biological sample is a tissue sample or is comprised of isolated nucleic acids such as mRNA, preferably the nucleic acids are amplified prior to the step of contacting the biological sample with the polynucleotide, preferably the polynucleotide is immobilized on a solid surface.

19. A method of affecting at least one bioactivity selected from angiogenesis and vasculogenesis in a vertebrate organism, said method comprising the step of administering to said organism an effective angiogenesis or vasculogenesis affecting amount of a nucleotide or polypeptide according to Claims 1 or 12, wherein the organism is preferably a mammal such as mice, rats, rabbits, guinea pigs, cats, dogs, pigs, cows, monkeys, and humans, wherein vasculogenesis or angiogenesis is preferably enhanced, increased, inhibited, or decreased, wherein the organism preferably has an angiogenesis-related disorder such as cancer, retinopathy, macular degeneration, corneal ulceration, stroke, ischemic heart disease, infertility, ulcers, scleradoma, wound healing, ischemia, ischemic heart disease, myocardial infarction, myocardosis, angina pectoris, unstable angina, coronary arteriosclerosis, arteriosclerosis obliterans, Berger's disease, arterial embolism, arterial thrombosis, cerebrovascular occlusion, cerebral infarction, cerebral thrombosis, cerebral embolism, rubeosis proliferative vitreoretinopathy, chronic inflammation, inflammatory bowel disease, psoriasis, sarcoidosis and rheumatoid arthritis.

20. A transgenic increased or decreased angiogenesis laboratory animal comprising one or more cells in which the expression of a sequence according to any one of SEQ ID NO:s 2, 4, 7, 9, 12, 14, 17, 19, 21, 24, 26, 29, 31, 34, 36, 39, 41, 44, 46, 49, 51, 54, and 56 is upregulated, downregulated, or absent.

Abstract

The present invention relates to polynucleotides and proteins associated with vasculogenesis- and angiogenesis-related disorders. The invention further relates to methods for the identification of compounds that modulate the expression of angiogenesis-related genes and gene products and to using such compounds as therapeutic agents in the treatment of angiogenesis-related disorders. The invention also relates to methods for the diagnostic evaluation, genetic testing and prognosis of angiogenesis-related disorders, and to methods and compositions for the treatment these disorders.

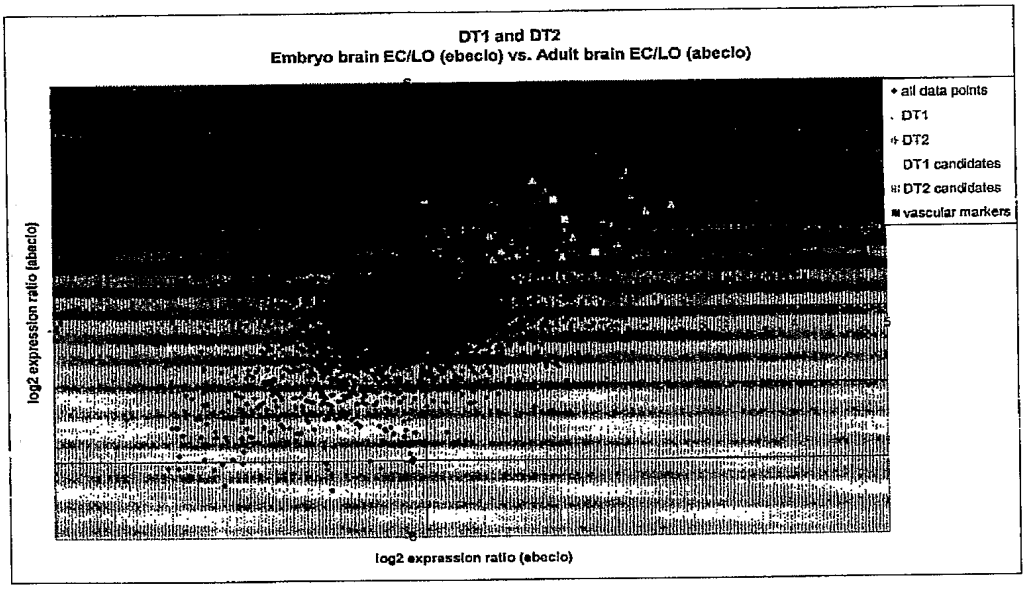


Figure 1

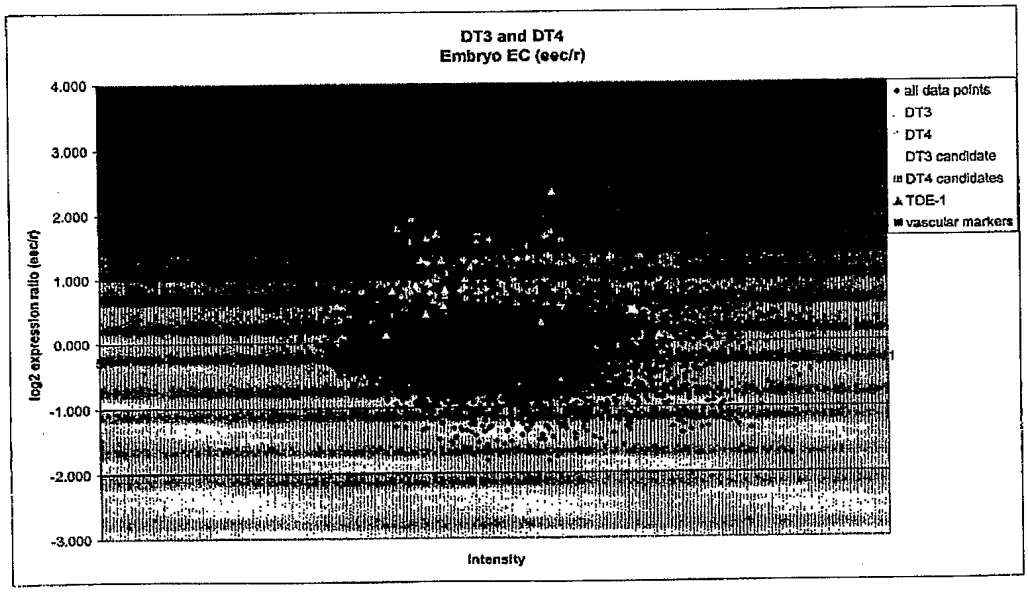


Figure 2

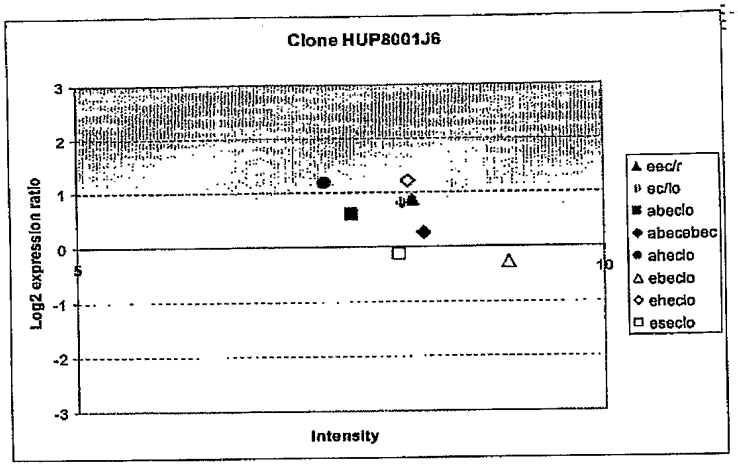


Figure 3

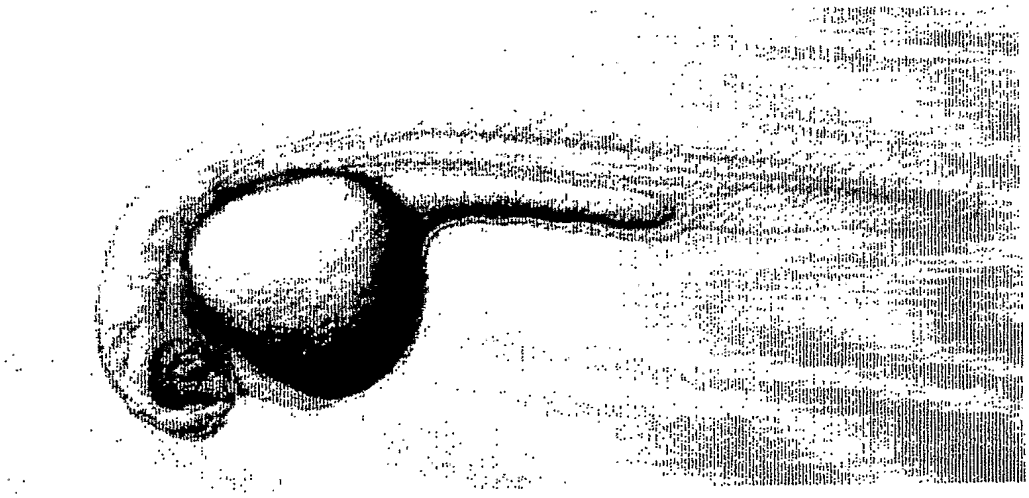
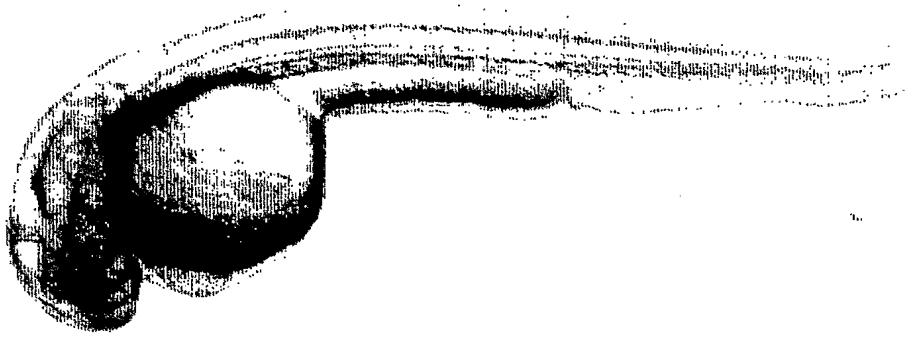


Figure 4



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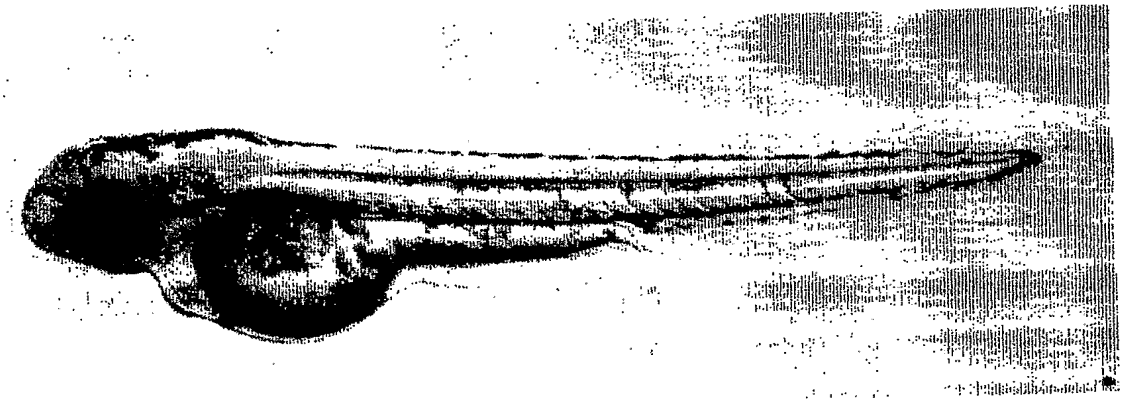

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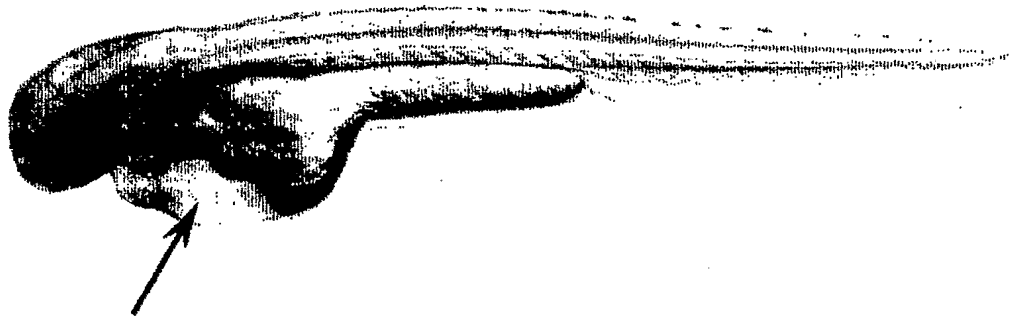

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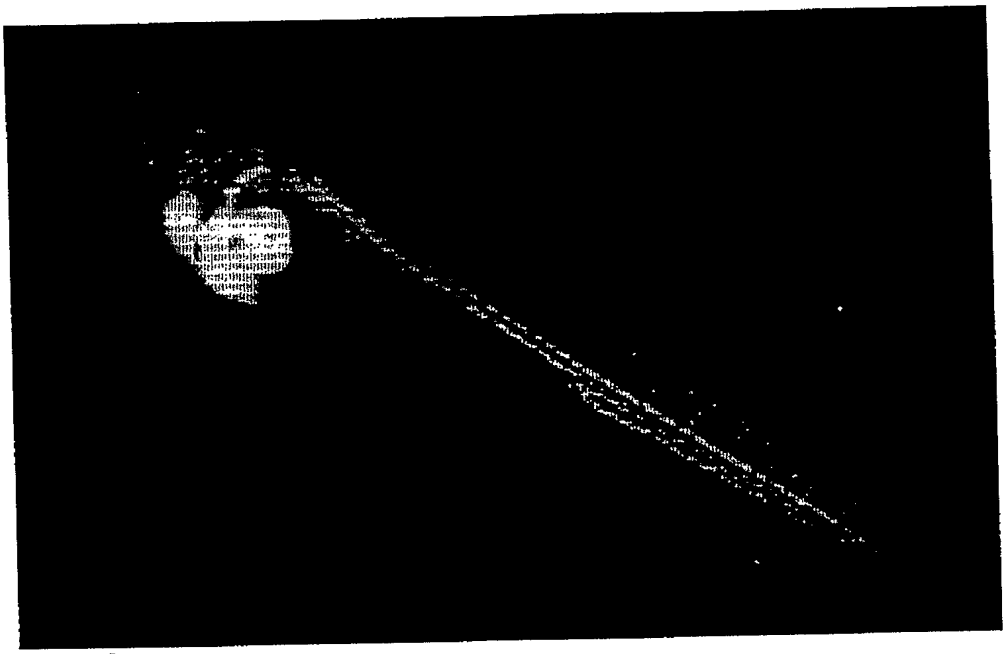

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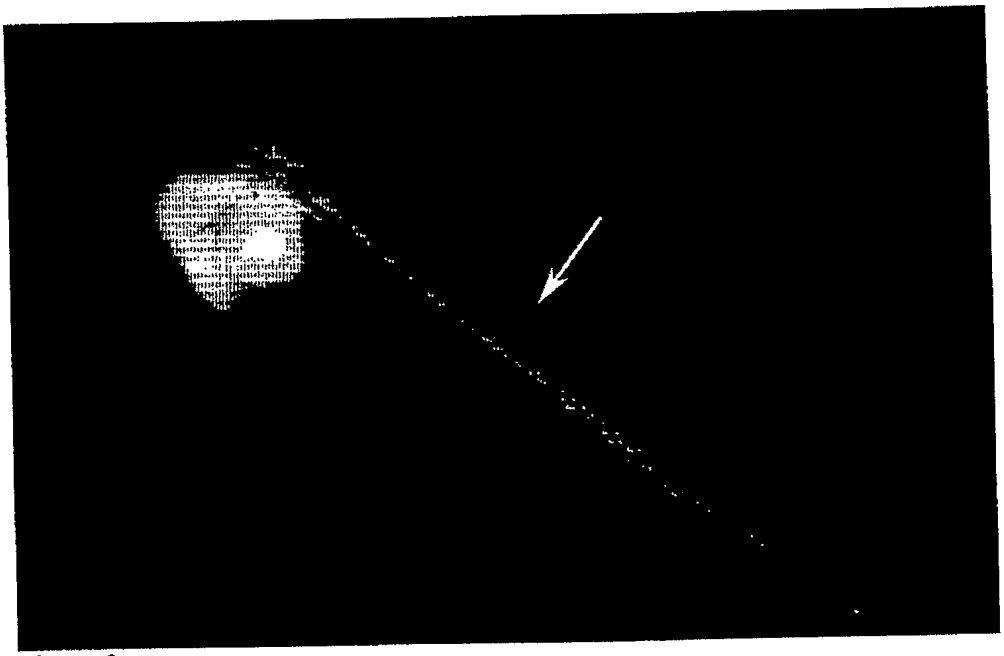

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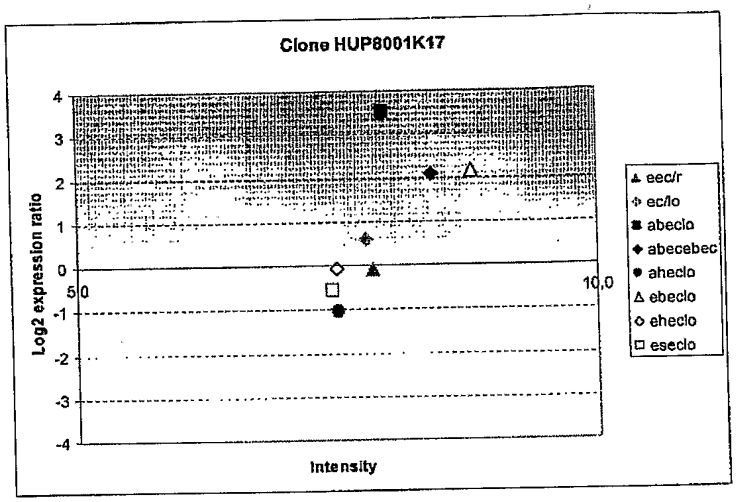

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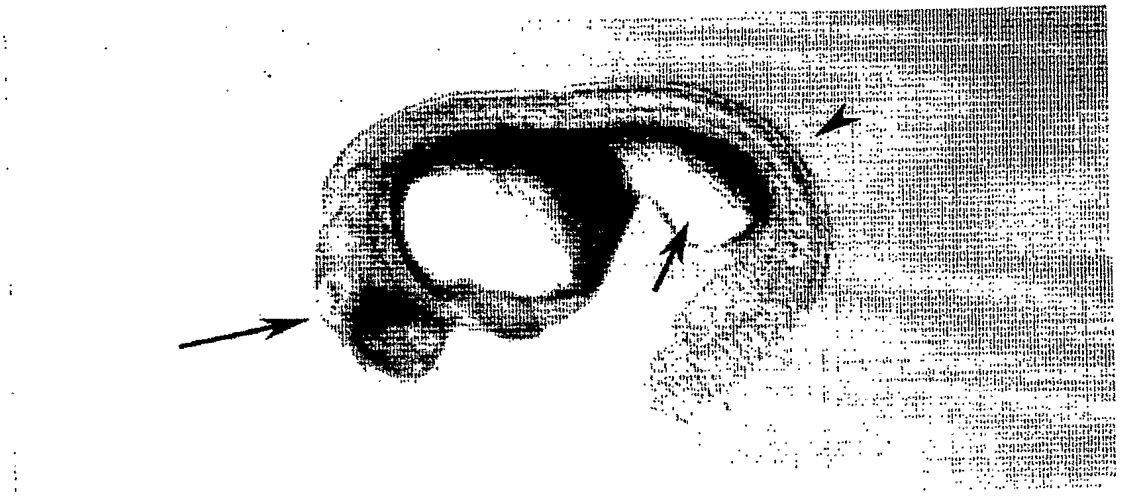

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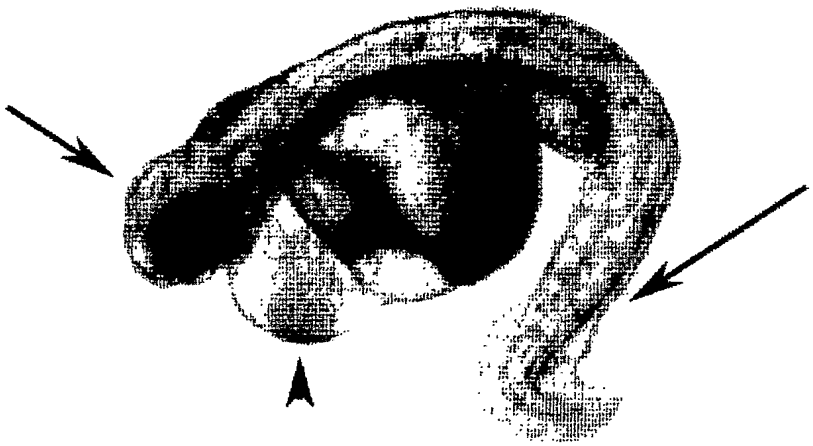

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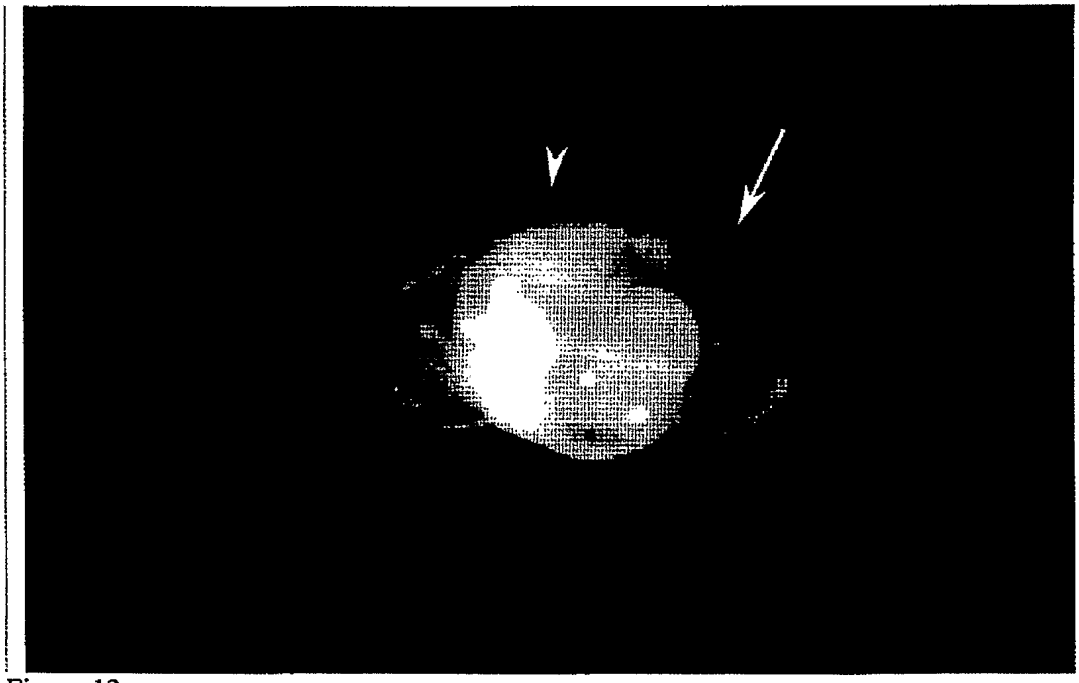

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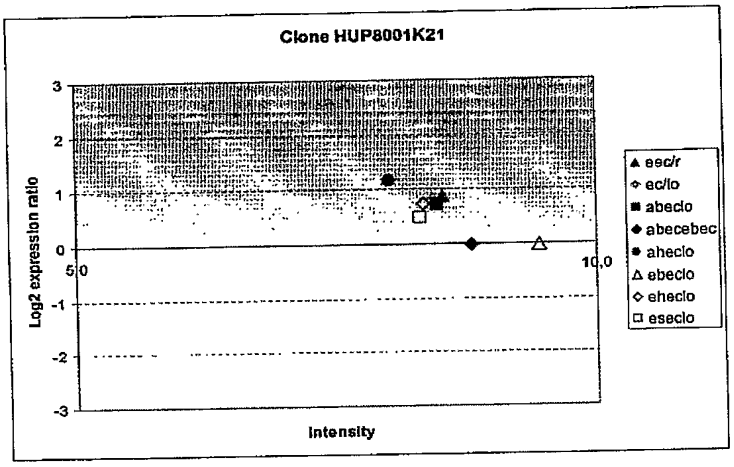

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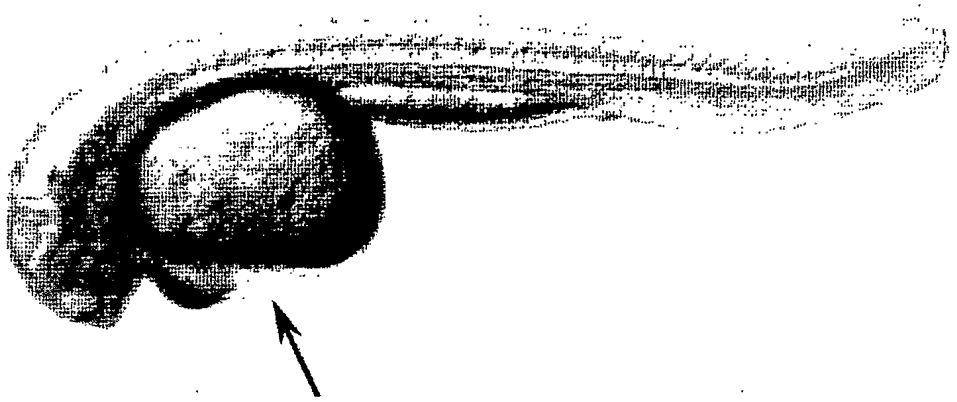

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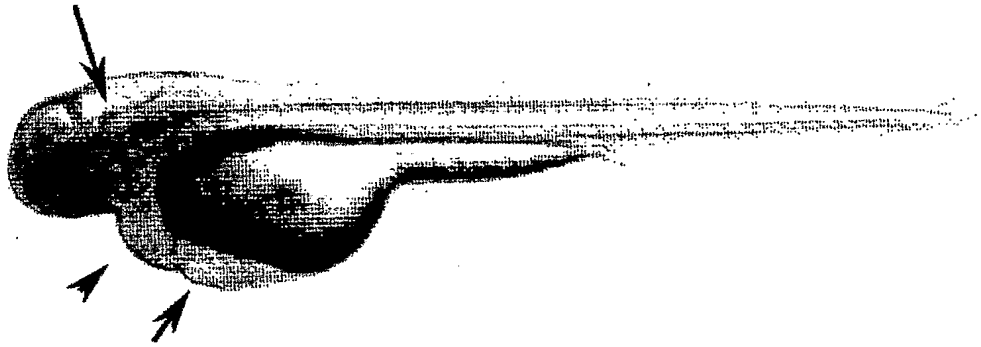

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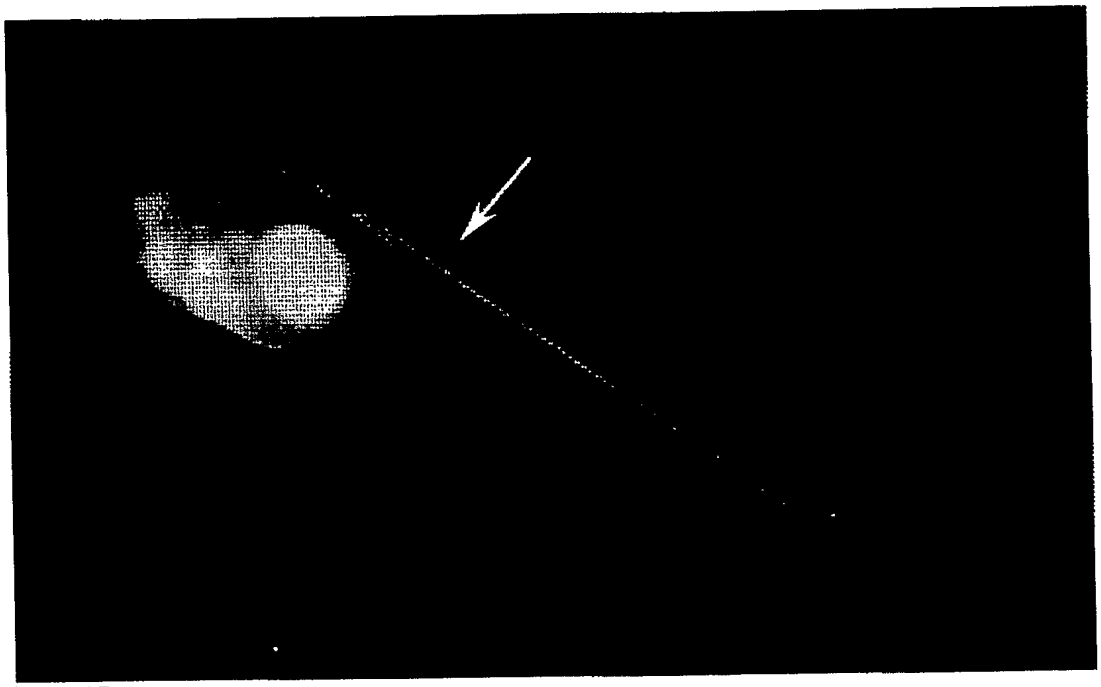

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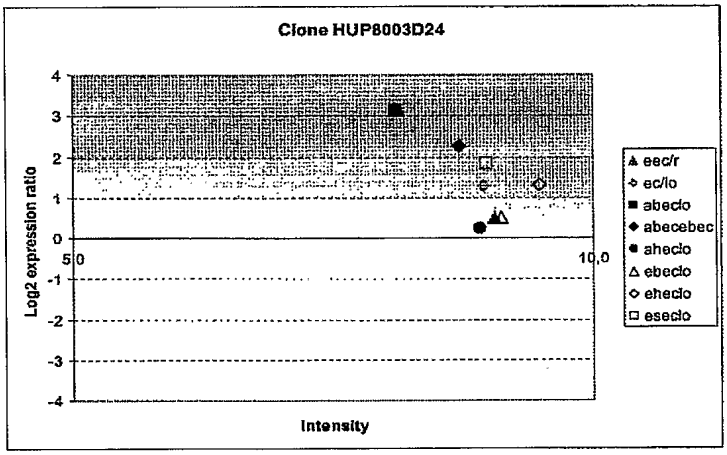

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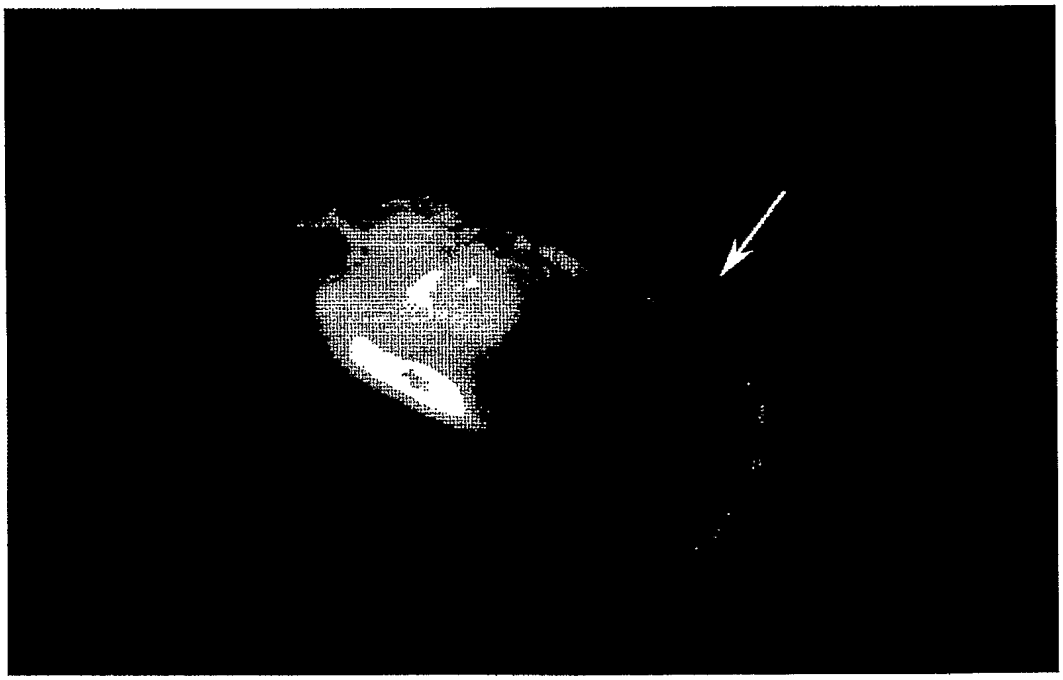

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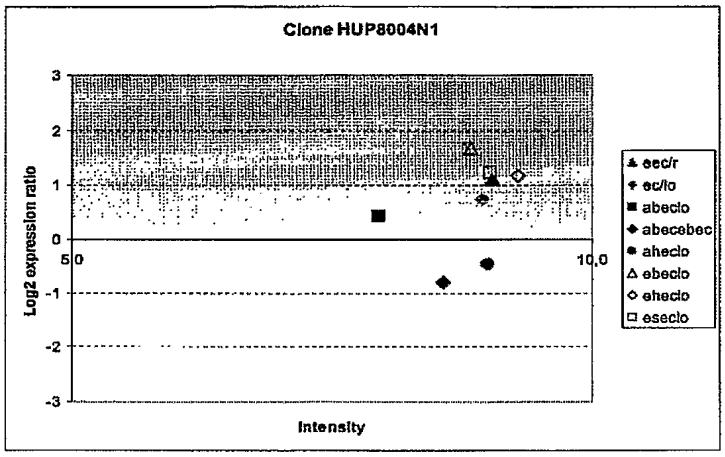

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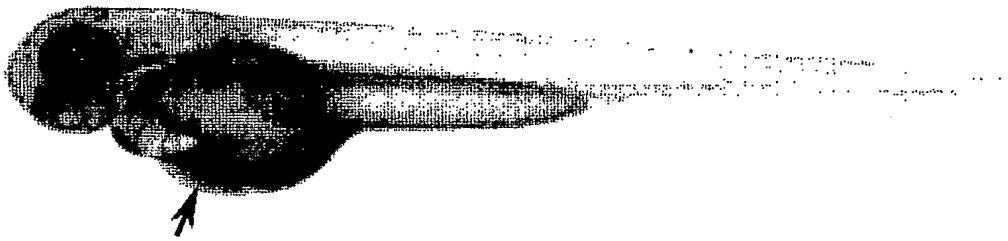

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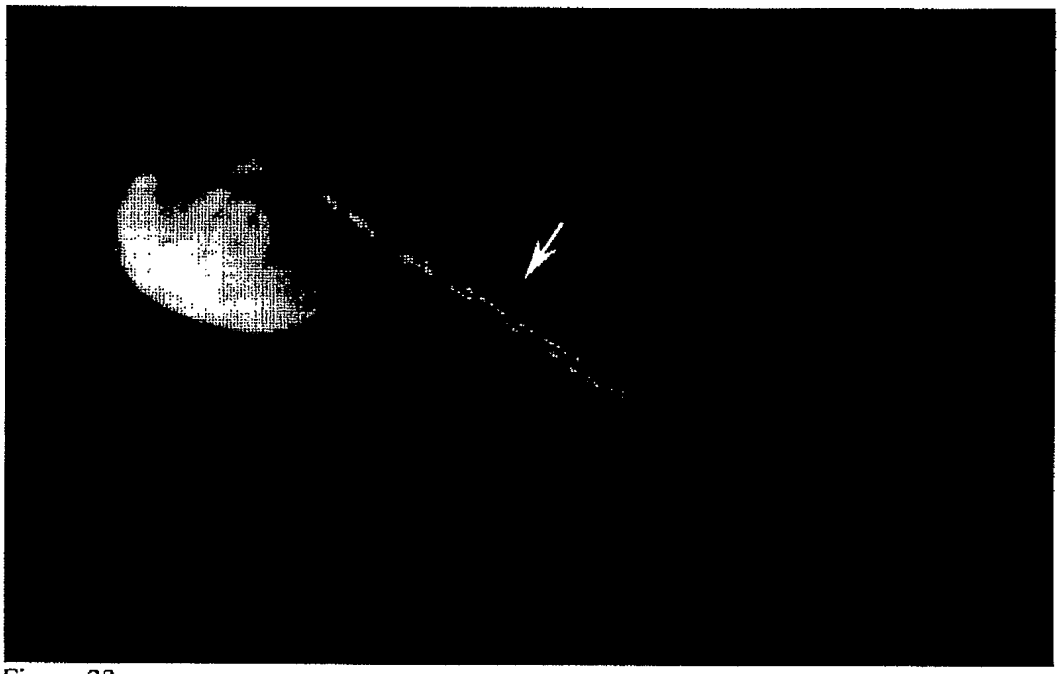

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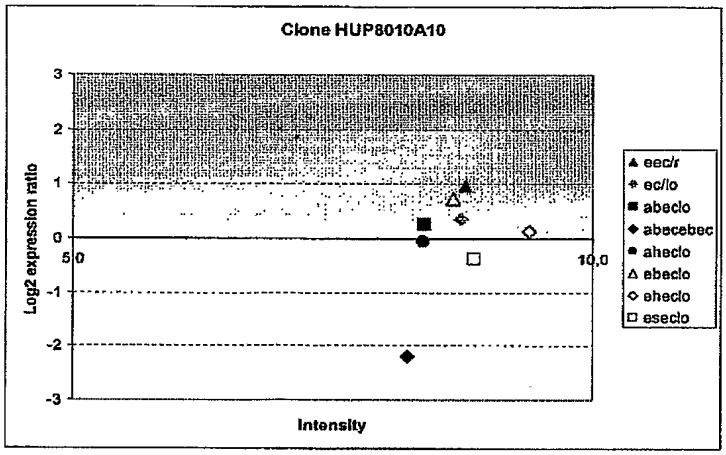

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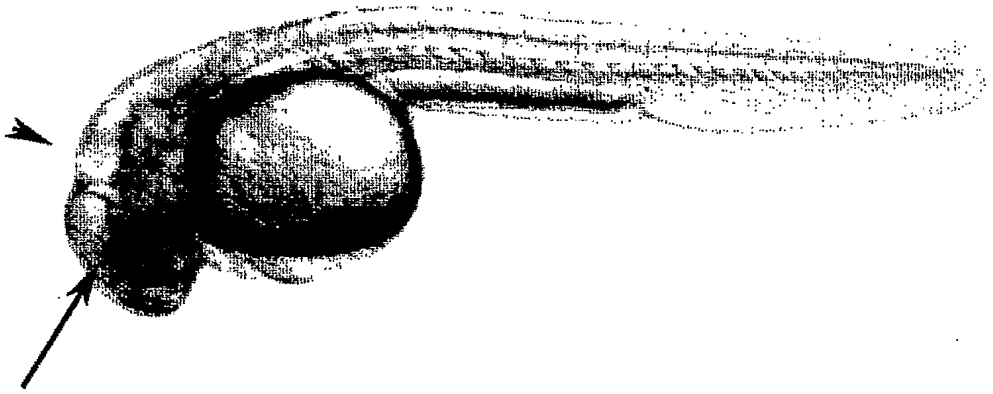

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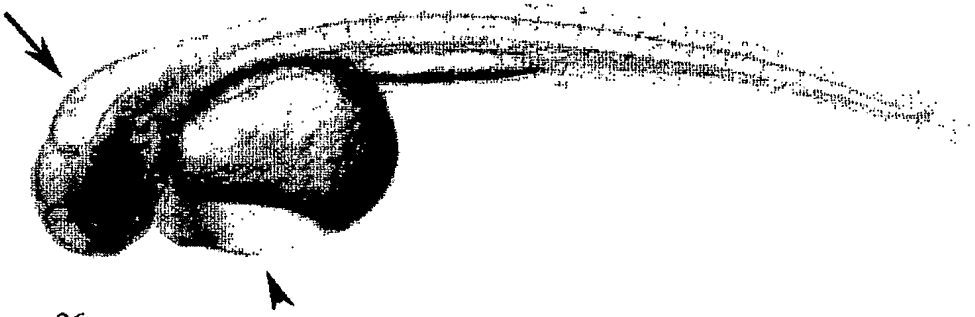

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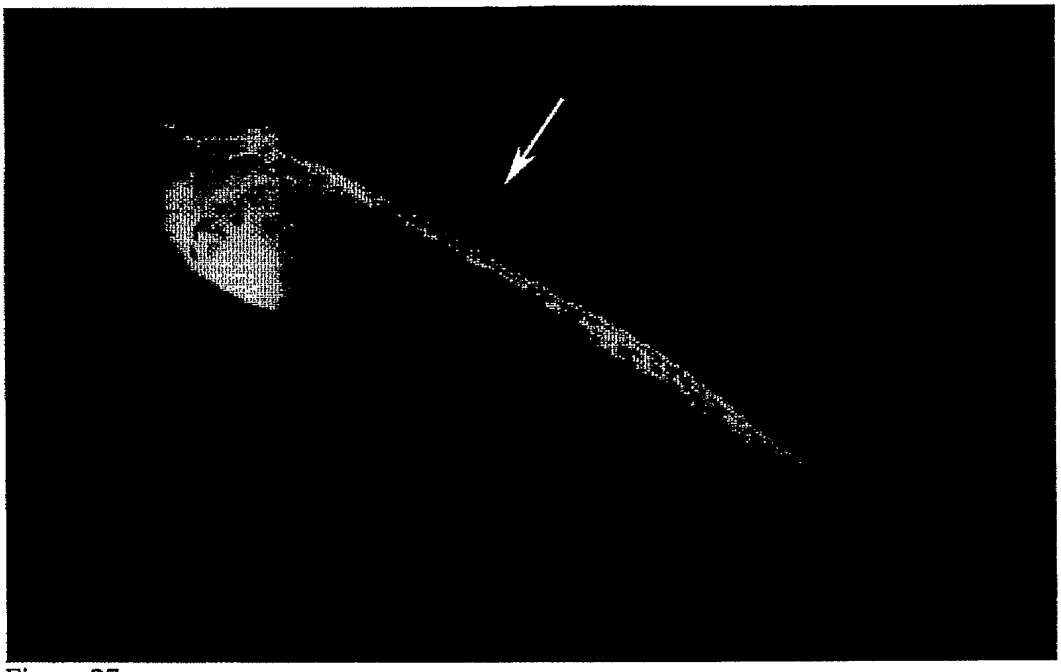

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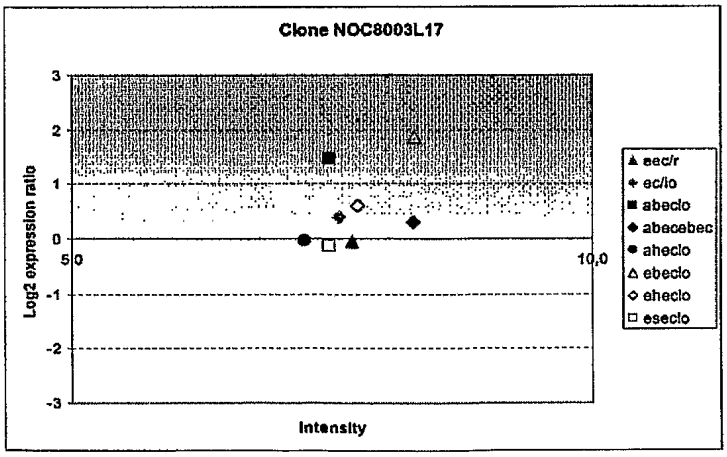

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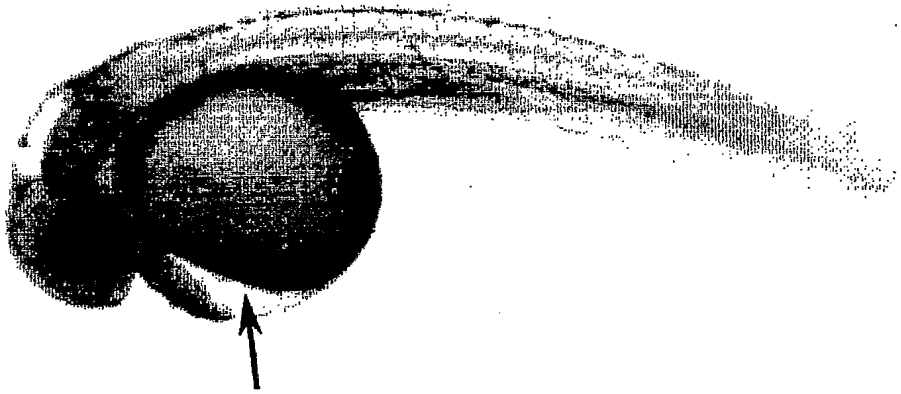

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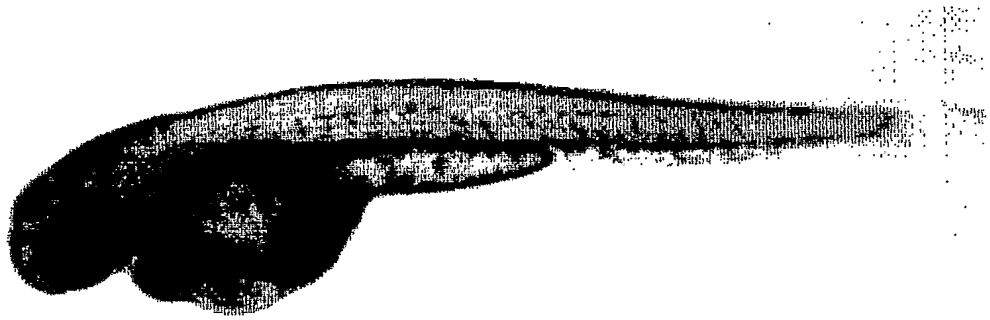

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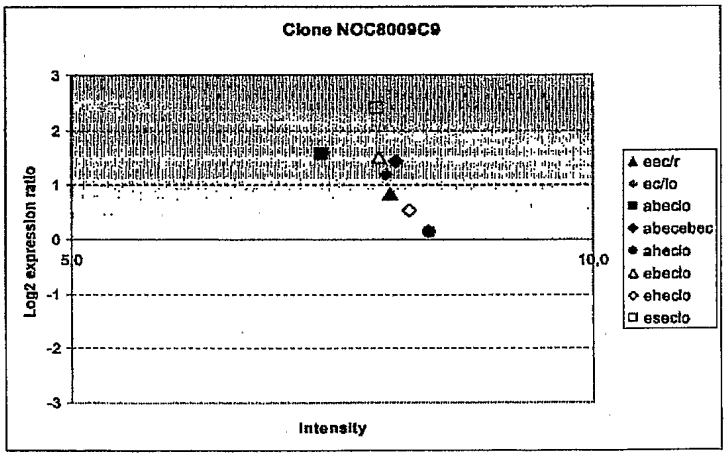

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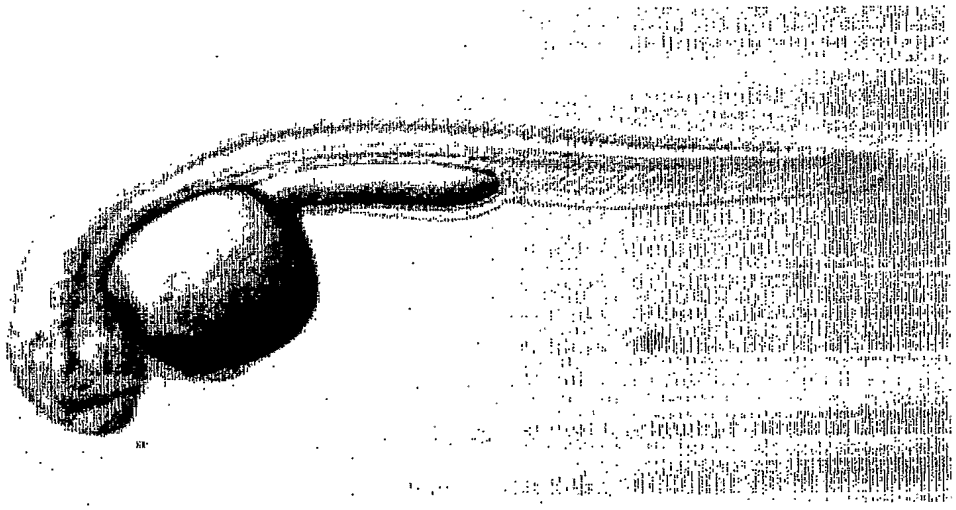

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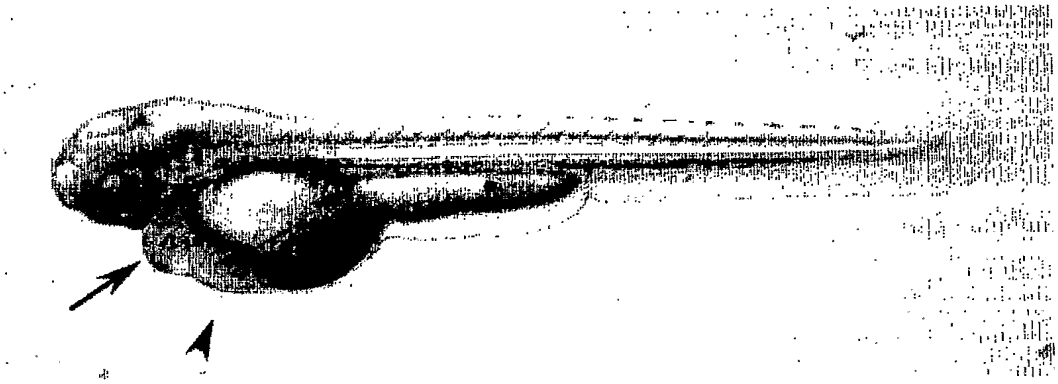

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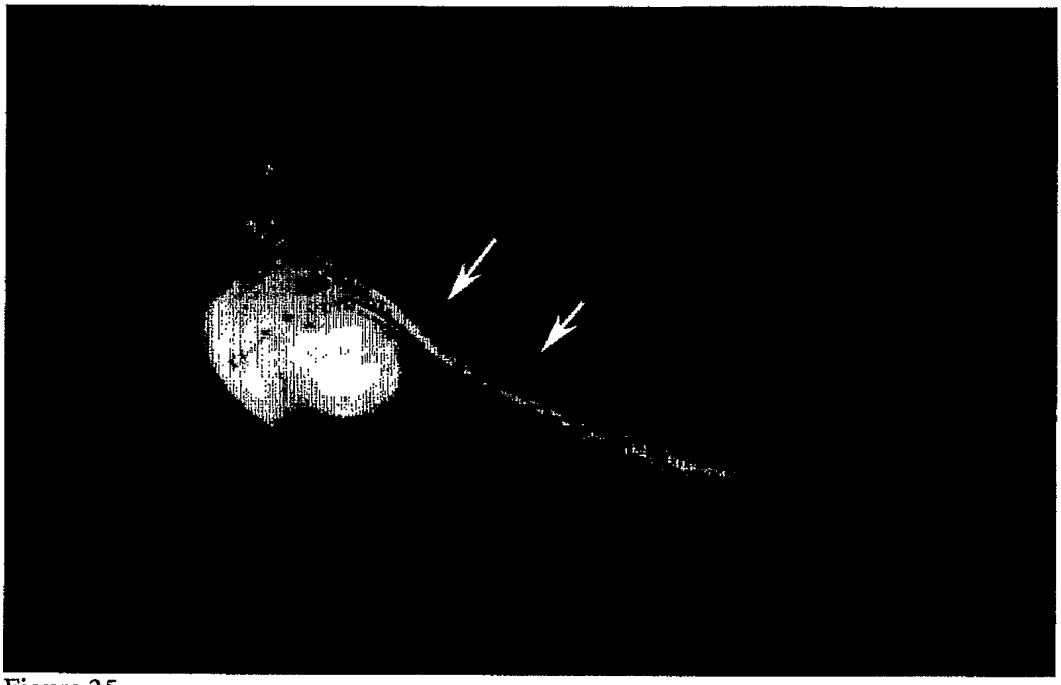

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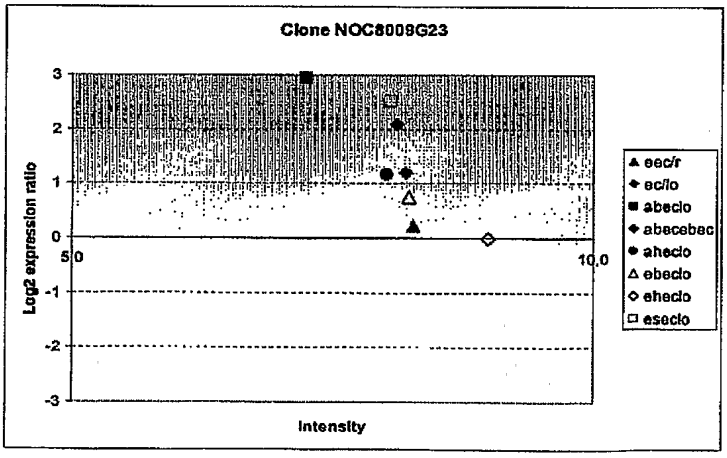

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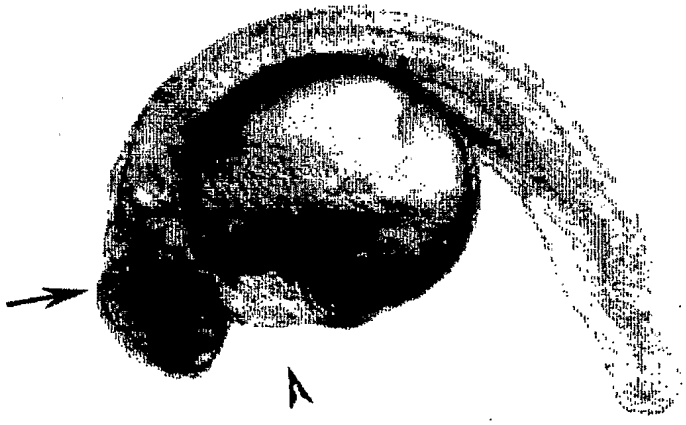

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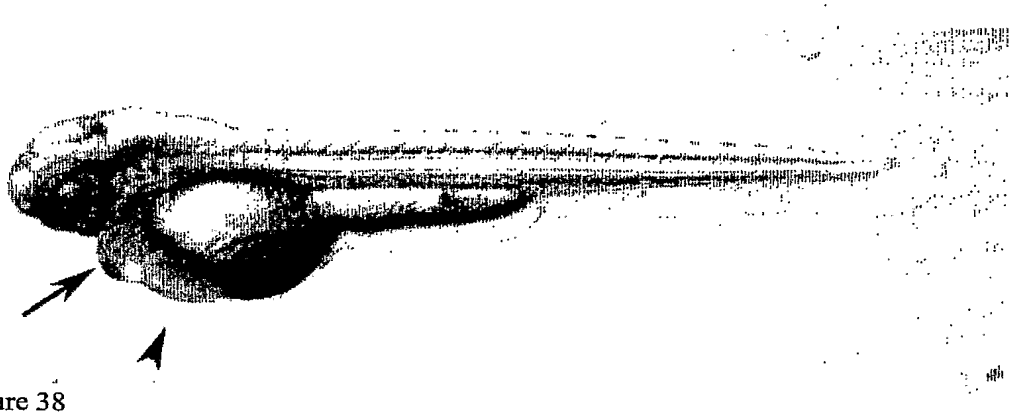

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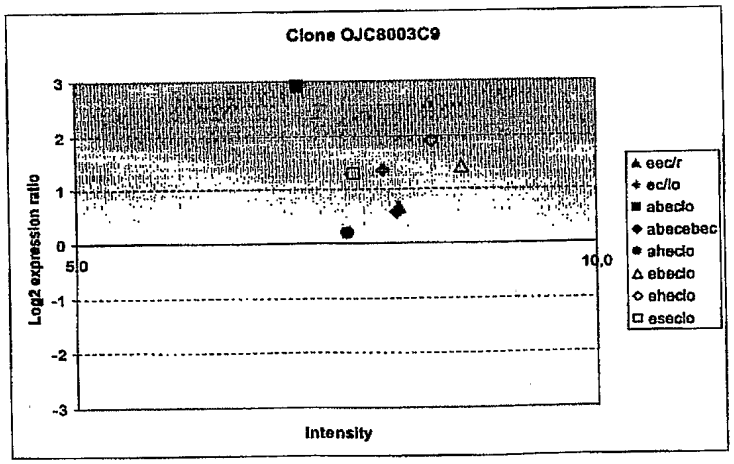

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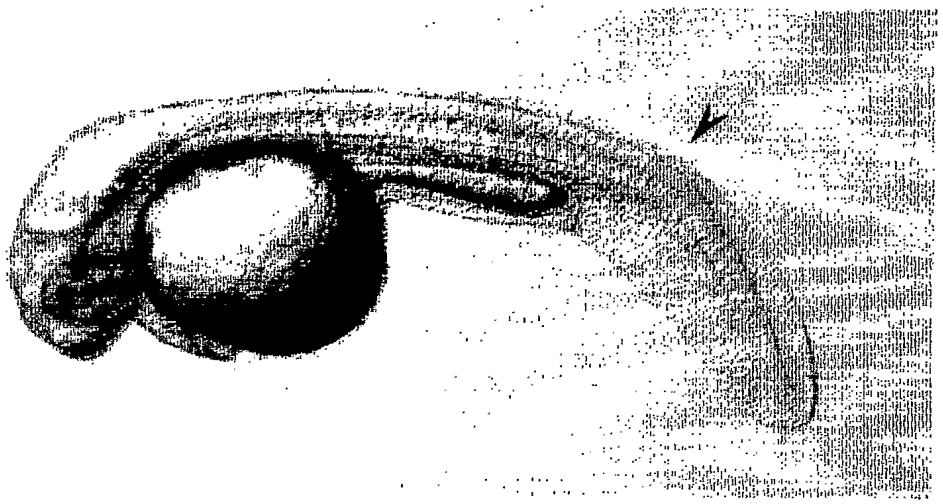

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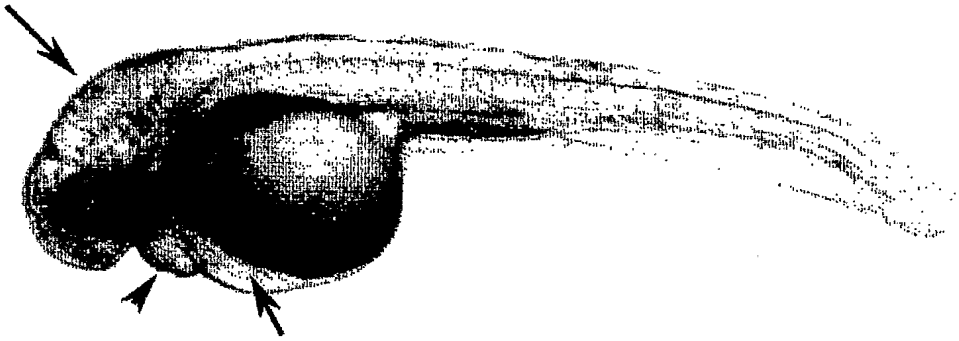

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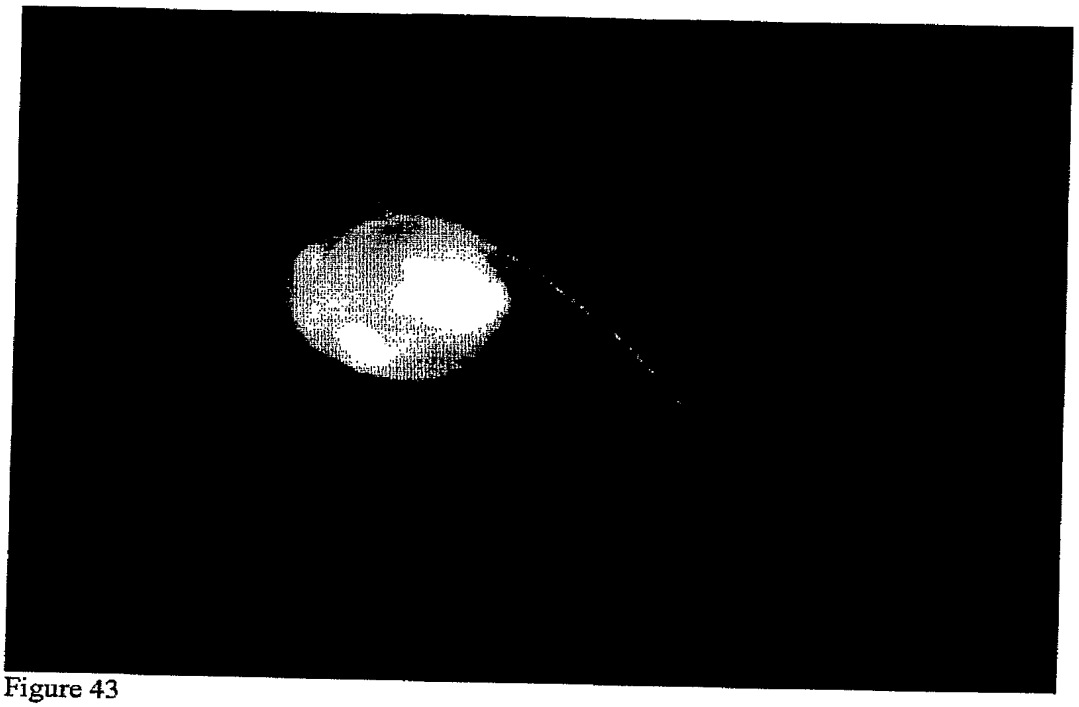

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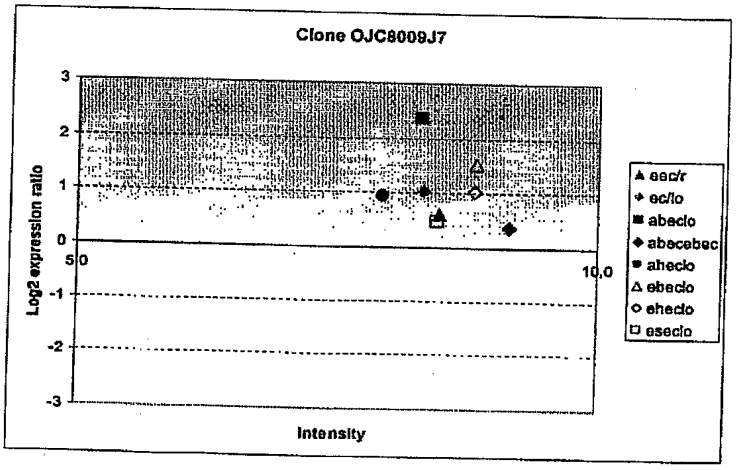

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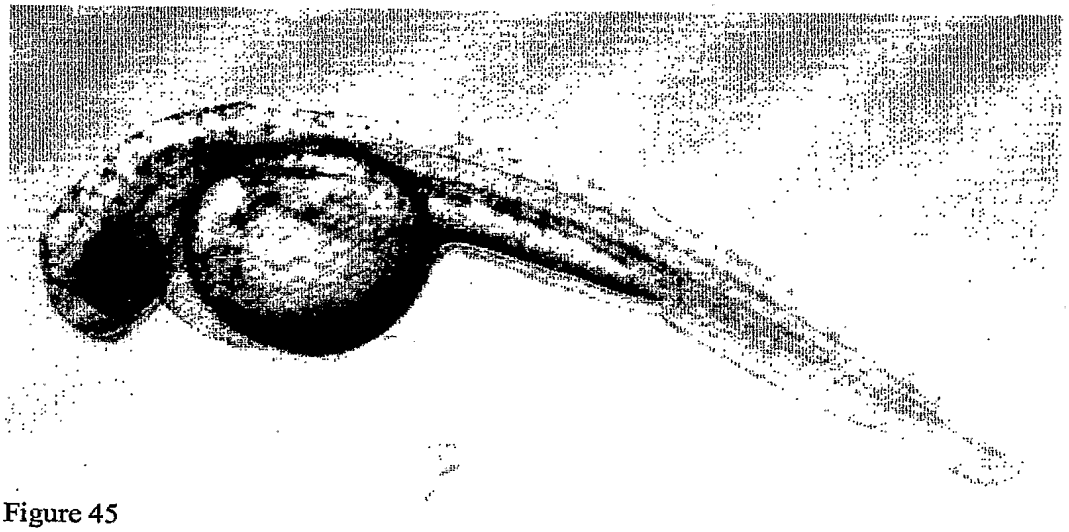

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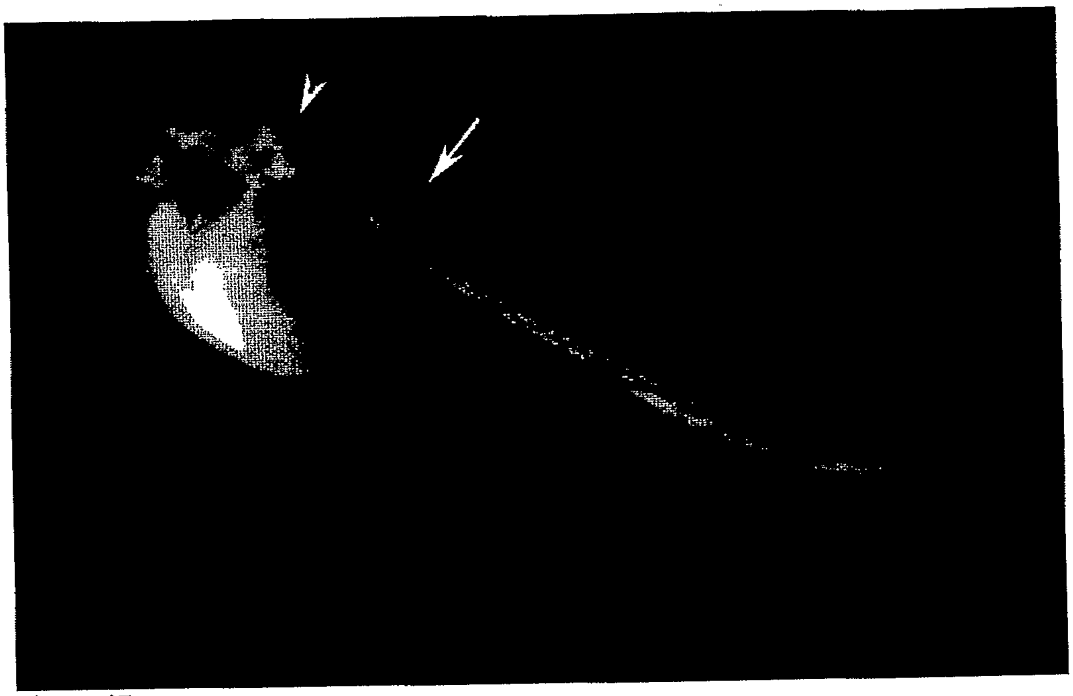

Figure 47

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<213> Homo sapiens

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Arg Glu Ile Leu Val Glu Glu Ser Asn Val Gln Arg Val Asp Ser Pro
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Val Thr Val Cys Gly Asp Ile His Gly Gln Phe Tyr Asp Leu Lys Glu
    50                  55                  60

Leu Phe Arg Val Gly Gly Asp Val Pro Glu Thr Asn Tyr Leu Phe Met
65                  70                  75                  80

Gly Asp Phe Val Asp Arg Gly Phe Tyr Ser Val Glu Thr Phe Leu Leu
                85                  90                  95

Leu Leu Ala Leu Lys Val Arg Tyr Pro Asp Arg Ile Thr Leu Ile Arg
            100                 105                 110

Gly Asn His Glu Ser Arg Gln Ile Thr Gln Val Tyr Gly Phe Tyr Asp
        115                 120                 125

Glu Cys Leu Arg Lys Tyr Gly Ser Val Thr Val Trp Arg Tyr Cys Thr
    130                 135                 140

Glu Ile Phe Asp Tyr Leu Ser Leu Ser Ala Ile Ile Asp Gly Lys Ile
145                 150                 155                 160

Phe Cys Val His Gly Gly Leu Ser Pro Ser Ile Gln Thr Leu Asp Gln
                165                 170                 175

Ile Arg Thr Ile Asp Arg Lys Gln Glu Val Pro His Asp Gly Pro Met
            180                 185                 190

Cys Asp Leu Leu Trp Ser Asp Pro Glu Asp Thr Thr Gly Trp Gly Val
        195                 200                 205

Ser Pro Arg Gly Ala Gly Tyr Leu Phe Gly Ser Asp Val Val Ala Gln
    210                 215                 220

Phe Asn Ala Ala Asn Asp Ile Asp Met Ile Cys Arg Ala His Gln Leu
225                 230                 235                 240
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Val Met Glu Gly Tyr Lys Trp His Phe Asn Glu Thr Val Leu Thr Val
245 250 255

Trp Ser Ala Pro Asn Tyr Cys Tyr Arg Cys Gly Asn Val Ala Ala Ile
260 265 270

Leu Glu Leu Asp Glu His Leu Gln Lys Asp Phe Ile Ile Phe Glu Ala
275 280 285

Ala Pro Gln Glu Thr Arg Gly Ile Pro Ser Lys Lys Pro Val Ala Asp
290 295 300

Tyr Phe Leu
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<212> DNA
<213> Murinae gen. sp.

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420

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480

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420

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<212> PRT
<213> Murinae gen. sp.

<400> 8

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Pro Ala Leu Trp Pro Phe Pro Arg Ser Val Gln Met Phe Pro Arg Leu
35 40 45

Leu Tyr Ile Ser Ala Glu Asp Phe Ser Ile Asp His Ser Pro Asn Ser
50 55 60

Thr Ala Gly Pro Ser Cys Ser Leu Leu Gln Glu Ala Phe Arg Arg Tyr
65 70 75 80

Tyr Asn Tyr Val Phe Gly Phe Tyr Lys Arg His His Gly Pro Ala Arg
85 90 95

Phe Arg Ala Glu Pro Gln Leu Gln Lys Leu Leu Val Ser Ile Thr Leu
100 105 110

Glu Ser Glu Cys Glu Ser Phe Pro Ser Leu Ser Ser Asp Glu Thr Tyr
115 120 125

Ser Leu Leu Val Gln Glu Pro Val Ala Val Leu Lys Ala Asn Ser Val
130 135 140

Trp Gly Ala Leu Arg Gly Leu Glu Thr Phe Ser Gln Leu Val Tyr Gln
145 150 155 160

Asp Ser Phe Gly Thr Phe Thr Ile Asn Glu Ser Ser Ile Ala Asp Ser
165 170 175

Pro Arg Phe Pro His Arg Gly Ile Leu Ile Asp Thr Ser Arg His Phe
180 185 190

Leu Pro Val Lys Thr Ile Leu Lys Thr Leu Asp Ala Met Ala Phe Asn
195 200 205

Lys Phe Asn Val Leu His Trp His Ile Val Asp Asp Gln Ser Phe Pro
210 215 220

Tyr Gln Ser Thr Thr Phe Pro Glu Leu Ser Asn Lys Gly Ser Tyr Ser
225 230 235 240

Leu Ser His Val Tyr Thr Pro Asn Asp Val Arg Met Val Leu Glu Tyr
245 250 255

Ala Arg Leu Arg Gly Ile Arg Val Ile Pro Glu Phe Asp Thr Pro Gly
260 265 270

His Thr Gln Ser Trp Gly Lys Gly Gln Lys Asn Leu Leu Thr Pro Cys
275 280 285

Tyr Asn Gln Lys Thr Lys Thr Gln Val Phe Gly Pro Val Asp Pro Thr
290 295 300

Val Asn Thr Thr Tyr Ala Phe Phe Asn Thr Phe Phe Lys Glu Ile Ser

305 310 315 320

Ser Val Phe Pro Asp Gln Phe Ile His Leu Gly Gly Asp Glu Val Glu
325 330 335

Phe Gln Cys Trp Ala Ser Asn Pro Asn Ile Gln Gly Phe Met Lys Arg
340 345 350

Lys Gly Phe Gly Ser Asp Phe Arg Arg Leu Glu Ser Phe Tyr Ile Lys
355 360 365

Lys Ile Leu Glu Ile Ile Ser Ser Leu Lys Lys Asn Ser Ile Val Trp
370 375 380

Gln Glu Val Phe Asp Asp Lys Val Glu Leu Gln Pro Gly Thr Val Val
385 390 395 400

Glu Val Trp Lys Ser Glu His Tyr Ser Tyr Glu Leu Lys Gln Val Thr
405 410 415

Gly Ser Gly Phe Pro Ala Ile Leu Ser Ala Pro Trp Tyr Leu Asp Leu
420 425 430

Ile Ser Tyr Gly Gln Asp Trp Lys Asn Tyr Tyr Lys Val Glu Pro Leu
435 440 445

Asn Phe Glu Gly Ser Glu Lys Gln Lys Gln Leu Val Ile Gly Gly Glu
450 455 460

Ala Cys Leu Trp Gly Glu Phe Val Asp Ala Thr Asn Leu Thr Pro Arg
465 470 475 480

Leu Trp Pro Arg Ala Ser Ala Val Gly Glu Arg Leu Trp Ser Pro Lys
485 490 495

Thr Val Thr Asp Leu Glu Asn Ala Tyr Lys Arg Leu Ala Val His Arg
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Cys Arg Met Val Ser Arg Gly Ile Ala Ala Gln Pro Leu Tyr Thr Gly
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<211> 1746

<212> DNA
<213> Homo sapiens

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240

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1746

<210> 10
<211> 556
<212> PRT
<213> Homo sapiens

<400> 10

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Val Ala Leu Val Val Gln Val Ala Glu Ala Ala Arg Ala Pro Ser Val
35 40 45

Ser Ala Lys Pro Gly Pro Ala Leu Trp Pro Leu Pro Leu Leu Val Lys
50 55 60

Met Thr Pro Asn Leu Leu His Leu Ala Pro Glu Asn Phe Tyr Ile Ser
65 70 75 80

His Ser Pro Asn Ser Thr Ala Gly Pro Ser Cys Thr Leu Leu Glu Glu
85 90 95

Ala Phe Arg Arg Tyr His Gly Tyr Ile Phe Gly Phe Tyr Lys Trp His
100 105 110

His Glu Pro Ala Glu Phe Gln Ala Lys Thr Gln Val Gln Gln Leu Leu
115 120 125

Val Ser Ile Thr Leu Gln Ser Glu Cys Asp Ala Phe Pro Asn Ile Ser
130 135 140

Ser Asp Glu Ser Tyr Thr Leu Leu Val Lys Glu Pro Val Ala Val Leu
145 150 155 160

Lys Ala Asn Arg Val Trp Gly Ala Leu Arg Gly Leu Glu Thr Phe Ser
165 170 175

Gln Leu Val Tyr Gln Asp Ser Tyr Gly Thr Phe Thr Ile Asn Glu Ser
180 185 190

Thr Ile Ile Asp Ser Pro Arg Phe Ser His Arg Gly Ile Leu Ile Asp
195 200 205

Thr Ser Arg His Tyr Leu Pro Val Lys Ile Ile Leu Lys Thr Leu Asp
210 215 220

Ala Met Ala Phe Asn Lys Phe Asn Val Leu His Trp His Ile Val Asp
225 230 235 240

Asp Gln Ser Phe Pro Tyr Gln Ser Ile Thr Phe Pro Glu Leu Ser Asn
245 250 255

Lys Gly Ser Tyr Ser Leu Ser His Val Tyr Thr Pro Asn Asp Val Arg
260 265 270

Met Val Ile Glu Tyr Ala Arg Leu Arg Gly Ile Arg Val Leu Pro Glu
275 280 285

Phe Asp Thr Pro Gly His Thr Leu Ser Trp Gly Lys Gly Gln Lys Asp
290 295 300

Leu Leu Thr Pro Cys Tyr Ser Arg Gln Asn Lys Leu Asp Ser Phe Gly
305 310 315 320

Pro Ile Asn Pro Thr Leu Asn Thr Thr Tyr Ser Phe Leu Thr Thr Phe

325 330 335

Phe Lys Glu Ile Ser Glu Val Phe Pro Asp Gln Phe Ile His Leu Gly
340 345 350

Gly Asp Glu Val Glu Phe Lys Cys Trp Glu Ser Asn Pro Lys Ile Gln
355 360 365

Asp Phe Met Arg Gln Lys Gly Phe Gly Thr Asp Phe Lys Lys Leu Glu
370 375 380

Ser Phe Tyr Ile Gln Lys Val Leu Asp Ile Ile Ala Thr Ile Asn Lys
385 390 395 400

Gly Ser Ile Val Trp Gln Glu Val Phe Asp Asp Lys Ala Lys Leu Ala
405 410 415

Pro Gly Thr Ile Val Glu Val Trp Lys Asp Ser Ala Tyr Pro Glu Glu
420 425 430

Leu Ser Arg Val Thr Ala Ser Gly Phe Pro Val Ile Leu Ser Ala Pro
435 440 445

Trp Tyr Leu Asp Leu Ile Ser Tyr Gly Gln Asp Trp Arg Lys Tyr Tyr
450 455 460

Lys Val Glu Pro Leu Asp Phe Gly Gly Thr Gln Lys Gln Lys Gln Leu
465 470 475 480

Phe Ile Gly Gly Glu Ala Cys Leu Trp Gly Glu Tyr Val Asp Ala Thr
485 490 495

Asn Leu Thr Pro Arg Leu Trp Pro Arg Ala Ser Ala Val Gly Glu Arg
500 505 510

Leu Trp Ser Ser Lys Asp Val Arg Asp Met Asp Asp Ala Tyr Asp Arg
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Leu Thr Arg His Arg Cys Arg Met Val Glu Arg Gly Ile Ala Ala Gln
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Pro Leu Tyr Ala Gly Tyr Cys Asn His Glu Asn Met
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<211> 676

<212> DNA
<213> Murinae gen. sp.

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120

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<210> 12
<211> 1369
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<213> Murinae gen. sp.

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180

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420

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<211> 330
<212> PRT
<213> Murinae gen. sp.

<400> 13

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20 25 30

Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg Glu Ile Phe Leu Ser
35 40 45

Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro Leu Lys Ile Cys Gly Asp
50 55 60

Ile His Gly Gln Tyr Tyr Asp Leu Leu Arg Leu Phe Glu Tyr Gly Gly
65 70 75 80

Phe Pro Pro Glu Ser Asn Tyr Leu Phe Leu Gly Asp Tyr Val Asp Arg
85 90 95

Gly Lys Gln Ser Leu Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile
100 105 110

Arg Tyr Pro Glu Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala
115 120 125

Ser Ile Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
130 135 140

Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys Leu Pro
145 150 155 160

Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His Gly Gly Leu
165 170 175

Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg Arg Ile Met Arg Pro
180 185 190

Thr Asp Val Pro Asp Gln Gly Leu Leu Cys Asp Leu Leu Trp Ser Asp
195 200 205

Pro Asp Lys Asp Val Gln Gly Trp Gly Glu Asn Asp Arg Gly Val Ser

210 215 220

Phe Thr Phe Gly Ala Glu Val Val Ala Lys Phe Leu His Lys His Asp
225 230 235 240

Leu Asp Leu Ile Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu
245 250 255

Phe Phe Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
260 265 270

Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp Glu Thr
275 280 285

Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Asp Lys Asn Lys Gly
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Pro Pro Arg Asn Ser Ala Lys Ala Lys Lys
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<210> 14
<211> 993
<212> DNA
<213> Homo sapiens

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360

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420

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780

cggcagctgg tgacactttt ctcagctccc aactactgtg gcgagtttga caatgctggc
840

gccatgatga gtgtggacga gaccctcatg tgctctttcc agatcctcaa gcccgccgac
900

aagaacaagg ggaagtacgg gcagttcagt ggcctgaacc ctggaggccg acccatcacc
960

ccaccccgca attccgccaa agccaagaaa tag
993

<210> 15
<211> 330
<212> PRT
<213> Homo sapiens

<400> 15

Met Ser Asp Ser Glu Lys Leu Asn Leu Asp Ser Ile Ile Gly Arg Leu
1 5 10 15

Leu Glu Val Gln Gly Ser Arg Pro Gly Lys Asn Val Gln Leu Thr Glu
20 25 30

Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg Glu Ile Phe Leu Ser
35 40 45

Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro Leu Lys Ile Cys Gly Asp
50 55 60

Ile His Gly Gln Tyr Tyr Asp Leu Leu Arg Leu Phe Glu Tyr Gly Gly
65 70 75 80

Phe Pro Pro Glu Ser Asn Tyr Leu Phe Leu Gly Asp Tyr Val Asp Arg
85 90 95

Gly Lys Gln Ser Leu Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile
100 105 110

FIG. 17B

Lys Tyr Pro Glu Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala
115 120 125

Ser Ile Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
130 135 140

Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys Leu Pro
145 150 155 160

Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His Gly Gly Leu
165 170 175

Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg Arg Ile Met Arg Pro
180 185 190

Thr Asp Val Pro Asp Gln Gly Leu Leu Cys Asp Leu Leu Trp Ser Asp
195 200 205

Pro Asp Lys Asp Val Gln Gly Trp Gly Glu Asn Asp Arg Gly Val Ser
210 215 220

Phe Thr Phe Gly Ala Glu Val Val Ala Lys Phe Leu His Lys His Asp
225 230 235 240

Leu Asp Leu Ile Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu
245 250 255

Phe Phe Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
260 265 270

Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp Glu Thr
275 280 285

Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Asp Lys Asn Lys Gly
290 295 300

Lys Tyr Gly Gln Phe Ser Gly Leu Asn Pro Gly Gly Arg Pro Ile Thr
305 310 315 320

Pro Pro Arg Asn Ser Ala Lys Ala Lys Lys
325 330

<210> 16
<211> 702
<212> DNA

<213> Murinae gen. sp.

<400> 16
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60

ggctgctgga gatatggctg tggtctacaa ggaggctggg gaactagcaa ggagatgctc
120

tctcagctat cacagcctta cagcaaagcc actatctctt tggattttga aattttctct
180

gccatgccta tgactatttt aaaattgggc aaagtatatc catttcagag gggctttttc
240

tgtactgaca acagcgtgaa gtacccgtac catgacagta ccatcccgtc ccgtatactc
300

gccatactgg ggcttggctt acccattttc tctatgagta tggagaatct ctgtctgttt
360

actttaatgt cttgcattcg aattcctttg tcggcaatcc ctacatagcc accatttaca
420

aagccgtcgg agccttttgt tcggagtctc agctagtcag tccttgactg acatcgctaa
480

gtatactata ggcagtttgc ggccgcactt cttggctatc tgtaacccag actggtcaaa
540

aatcaactgc agtgatggct atattgagga ctacatatgt caagggaatg aagagaaagt
600

caaggagggc aggttgtctt tctactcggg acactcttca ttctctatgt actgcatgct
660

gtttgtcgca ctttatcttc aagccaggat gaagggagac tg
702

<210> 17
<211> 1432
<212> DNA
<213> Murinae gen. sp.

<400> 17
catccttaga gctcgcccgg cctgttggag agggcacagg gcagcggagg gcgattggcc
60

gcgacgagcc agcactgaga gagcaggcgc ctgaggcgac agatcggcgg ccactcggtg
120

gcagggcggc ccaatccaaa ctgccctggt ccctgctccc gtcagtctaa gaggctcgca
180

gtcgcttggg gcggccgcca tcccgagggc ggggctctgg gaattgggta tctggaccgc
240

cgcggtctgt tcctcccgcc actcgcacca ggtggtgaca ccatccagcc ggtgaccatg
300

ttcgacaaga cgcggctgcc gtacgtggcc ctcgatgtga tttgcgtgtt gctggctgga
360

ttgccttttg caattcttac ttcaaggcat acccccttcc agcgaggaat attctgtaat
420

gatgactcca tcaagtaccc ttacaaggaa gacaccatac cttatgcctt attaggtgga
480

atagtcattc cattctgtat tatcgttatg agtattggag aatctctgtc tgtttacttt
540

aatgtcttgc attcgaattc ctttgtcggc aatccctaca tagccaccat ttacaaagcc
600

gtcggagcct ttttgttcgg agtctcagct agtcagtcct tgactgacat cgctaagtat
660

actataggca gtttgcggcc gcacttcttg gctatctgta acccagactg gtcaaaaatc
720

aactgcagtg atggctatat tgaggactac atatgtcaag ggaatgaaga gaaagtcaag
780

gagggcaggt tgtctttcta ctcgggacac tcttcattct ctatgtactg catgctgttt
840

gtcgcacttt atcttcaagc caggatgaag ggagactggg caagactctt acgacccatg
900

ctccagtttg ggctcattgc ttttttccata tatgtgggcc tttctcgagt gtctgactac
960

aaacaccact ggagtgacgt cacagttgga ctcattcagg gagctgctat ggctatactg
1020

gttgctttgt atgtatccga tttcttcaag gacacacatt cttacaaaga gagaaaggaa
1080

gaggatccac acacgactct ccatgaaacc gccagttcac ggaactactg ggcgctggcc
1140

cgcttcaaag gcaacagctg gaggctaaag gcaggggat gcgtattact tcctgctgta
1200

cagaccattc tataaaggac tgctgctatc tatacctcct ggatgcccat tttatgtgtg
1260

tacagttact tctaacacaa tgagtaacag ttcaattaaa gaaaatgaag cctgtcacta
1320

aaacactgtc ccacctgtac atttttattg aaagacgcta tgtacaaatg tgtatgttac
1380

atgccttctc agaatgatgt tgacttaaat ataataaaaa gcttgtgaac ca
1432

<210> 18
<211> 378
<212> PRT

<213> Murinae gen. sp.

<400> 18

Glu Ser Arg Arg Leu Arg Arg Gln Ile Gly Gly His Ser Val Ala Gly
1 5 10 15

Arg Pro Asn Pro Asn Cys Pro Gly Pro Cys Ser Arg Gln Ser Lys Arg
20 25 30

Leu Ala Val Ala Trp Gly Gly Arg His Pro Glu Gly Gly Ala Leu Gly
35 40 45

Ile Gly Tyr Leu Asp Arg Arg Gly Leu Phe Leu Pro Pro Leu Ala Pro
50 55 60

Gly Gly Asp Thr Ile Gln Pro Val Thr Met Phe Asp Lys Thr Arg Leu
65 70 75 80

Pro Tyr Val Ala Leu Asp Val Ile Cys Val Leu Leu Ala Gly Leu Pro
85 90 95

Phe Ala Ile Leu Thr Ser Arg His Thr Pro Phe Gln Arg Gly Ile Phe
100 105 110

Cys Asn Asp Asp Ser Ile Lys Tyr Pro Tyr Lys Glu Asp Thr Ile Pro
115 120 125

Tyr Ala Leu Leu Gly Gly Ile Val Ile Pro Phe Cys Ile Ile Val Met
130 135 140

Ser Ile Gly Glu Ser Leu Ser Val Tyr Phe Asn Val Leu His Ser Asn
145 150 155 160

Ser Phe Val Gly Asn Pro Tyr Ile Ala Thr Ile Tyr Lys Ala Val Gly
165 170 175

Ala Phe Leu Phe Gly Val Ser Ala Ser Gln Ser Leu Thr Asp Ile Ala
180 185 190

Lys Tyr Thr Ile Gly Ser Leu Arg Pro His Phe Leu Ala Ile Cys Asn
195 200 205

Pro Asp Trp Ser Lys Ile Asn Cys Ser Asp Gly Tyr Ile Glu Asp Tyr
210 215 220

Ile Cys Gln Gly Asn Glu Glu Lys Val Lys Glu Gly Arg Leu Ser Phe

225 230 235 240

Tyr Ser Gly His Ser Ser Phe Ser Met Tyr Cys Met Leu Phe Val Ala
245 250 255

Leu Tyr Leu Gln Ala Arg Met Lys Gly Asp Trp Ala Arg Leu Leu Arg
260 265 270

Pro Met Leu Gln Phe Gly Leu Ile Ala Phe Ser Ile Tyr Val Gly Leu
275 280 285

Ser Arg Val Ser Asp Tyr Lys His His Trp Ser Asp Val Thr Val Gly
290 295 300

Leu Ile Gln Gly Ala Ala Met Ala Ile Leu Val Ala Leu Tyr Val Ser
305 310 315 320

Asp Phe Phe Lys Asp Thr His Ser Tyr Lys Glu Arg Lys Glu Glu Asp
325 330 335

Pro His Thr Thr Leu His Glu Thr Ala Ser Ser Arg Asn Tyr Trp Ala
340 345 350

Leu Ala Arg Phe Lys Gly Asn Ser Trp Arg Leu Lys Ala Gly Gly Cys
355 360 365

Val Leu Leu Pro Ala Val Gln Thr Ile Leu
370 375

<210> 19
<211> 1626
<212> DNA
<213> Homo sapiens

<400> 19
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60

gagtctggac gccccgcctg tgggagagag cgccgggatc cggacgggga gcaaccgggg
120

caggccgtgc cggctgagga ggtcctgagg ctacagagct gccgcggctg gcacacgagc
180

gcctcggcac taaccgagtg ttcgcggggg ctgtgagggg agggccccgg gcgccattgc
240

tggcggtggg agcgccgccc ggtctcagcc cgccctcggc tgctctcctc ctccggctgg
300

gaggggccgt agctcggggc cgtcgccagc cccggcccgg gctcgagaat caagggcctc
360

ggccgccgtc ccgcagctca gtccatcgcc cttgccgggc agcccgggca gagaccatgt
420

ttgacaagac gcggctgccg tacgtggccc tcgatgtgct ctgcgtgttg ctggcttcca
480

tgcctatggc tgttctaaaa ttgggccaaa tatatccatt tcagagaggc tttttctgta
540

aagacaacag catcaactat ccgtaccatg acagtaccgt cacatccact gtcctcatcc
600

tagtgggggt tggcttgccc atttcctcta ttattcttgg agaaaccctg tctgtttact
660

gtaacctttt gcactcaaat tcctttatca ggaataacta catagccact atttacaaag
720

ccattggaac ctttttattt ggtgcagctg ctagtcagtc cctgactgac attgccaagt
780

attcaatagg cagactgcgg cctcacttct tggatgtttg tgatccagat tggtcaaaaa
840

tcaactgcag cgatggttac attgaatact acatatgtcg agggaatgca gaaagagtta
900

aggaaggcag gttgtccttc tattcaggcc actcttcgtt ttccatgtac tgcatgctgt
960

ttgtggcact ttatcttcaa gccaggatga agggagactg ggcaagactc ttacgcccca
1020

cactgcaatt tggtcttgtt gccgtatcca tttatgtggg cctttctcga gtttctgatt
1080

ataaacacca ctggagcgat gtgttgactg gactcattca gggagctctg gttgcaatat
1140

tagttgctgt atatgtatcg gatttcttca aagaaagaac ttcttttaaa gaaagaaaag
1200

aggaggactc tcatacaact ctgcatgaaa caccaacaac tgggaatcac tatccgagca
1260

atcaccagcc ttgaaaggca gcagggtgcc caggtgaagc tggcctgttt tctaaaggaa
1320

aatgattgcc acaaggcaag aggatgcatc tttcttcctg gtgtacaagc ctttaaagac
1380

ttctgctgct gctatgcctc ttggatgcac actttgtgtg tacatagtta cctttaactc
1440

agtggttatc taatagctct aaactcatta aaaaaactcc aagccttcca ccaaaacagt
1500

gccccacctg tatacatttt tattaaaaaa atgtaatgct tatgtataaa catgtatgta
1560

atatgctttc tatgaatgat gtttgattta aatataatac atattaaaat gtatgggaga
1620

accaaa
1626

<210> 20
<211> 378
<212> PRT
<213> Homo sapiens

<400> 20

Gly Gly Pro Glu Ala Thr Glu Leu Pro Arg Leu Ala His Glu Arg Leu
1 5 10 15

Gly Thr Asn Arg Val Phe Ala Gly Ala Val Arg Gly Gly Pro Arg Ala
20 25 30

Pro Leu Leu Ala Val Gly Ala Pro Pro Gly Leu Ser Pro Pro Ser Ala
35 40 45

Ala Leu Leu Leu Arg Leu Gly Gly Ala Val Ala Arg Gly Arg Arg Gln
50 55 60

Pro Arg Pro Gly Leu Glu Asn Gln Gly Pro Arg Pro Pro Ser Arg Ser
65 70 75 80

Ser Val His Arg Pro Cys Arg Ala Ala Arg Ala Glu Thr Met Phe Asp
85 90 95

Lys Thr Arg Leu Pro Tyr Val Ala Leu Asp Val Leu Cys Val Leu Leu
100 105 110

Ala Ser Met Pro Met Ala Val Leu Lys Leu Gly Gln Ile Tyr Pro Phe
115 120 125

Gln Arg Gly Phe Phe Cys Lys Asp Asn Ser Ile Asn Tyr Pro Tyr His
130 135 140

Asp Ser Thr Val Thr Ser Thr Val Leu Ile Leu Val Gly Val Gly Leu
145 150 155 160

Pro Ile Ser Ser Ile Ile Leu Gly Glu Thr Leu Ser Val Tyr Cys Asn
165 170 175

Leu Leu His Ser Asn Ser Phe Ile Arg Asn Asn Tyr Ile Ala Thr Ile
180 185 190

Tyr Lys Ala Ile Gly Thr Phe Leu Phe Gly Ala Ala Ala Ser Gln Ser
195 200 205

Leu Thr Asp Ile Ala Lys Tyr Ser Ile Gly Arg Leu Arg Pro His Phe
210 215 220

Leu Asp Val Cys Asp Pro Asp Trp Ser Lys Ile Asn Cys Ser Asp Gly
225 230 235 240

Tyr Ile Glu Tyr Tyr Ile Cys Arg Gly Asn Ala Glu Arg Val Lys Glu
245 250 255

Gly Arg Leu Ser Phe Tyr Ser Gly His Ser Ser Phe Ser Met Tyr Cys
260 265 270

Met Leu Phe Val Ala Leu Tyr Leu Gln Ala Arg Met Lys Gly Asp Trp
275 280 285

Ala Arg Leu Leu Arg Pro Thr Leu Gln Phe Gly Leu Val Ala Val Ser
290 295 300

Ile Tyr Val Gly Leu Ser Arg Val Ser Asp Tyr Lys His His Trp Ser
305 310 315 320

Asp Val Leu Thr Gly Leu Ile Gln Gly Ala Leu Val Ala Ile Leu Val
325 330 335

Ala Val Tyr Val Ser Asp Phe Phe Lys Glu Arg Thr Ser Phe Lys Glu
340 345 350

Arg Lys Glu Glu Asp Ser His Thr Thr Leu His Glu Thr Pro Thr Thr
355 360 365

Gly Asn His Tyr Pro Ser Asn His Gln Pro
370 375

<210> 21
<211> 816
<212> DNA
<213> Homo sapiens

<400> 21
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60

ttccaacgag gagtattctg taatgatgag tccatcaagt acccttacaa agaagacacc
120

ataccttatg cgttattagg tggaataatc attccattca gtattatcgt tattattctt
180

ggagaaaccc tgtctgttta ctgtaacctt ttgcactcaa attcctttat caggaataac
240

tacatagcca ctatttacaa agccattgga acctttttat ttggtgcagc tgctagtcag
300

tccctgactg acattgccaa gtattcaata ggcagactgc ggcctcactt cttggatgtt
360

tgtgatccag attggtcaaa aatcaactgc agcgatggtt acattgaata ctacatatgt
420

cgagggaatg cagaaagagt taaggaaggc aggttgtcct tctattcagg ccactcttcg
480

ttttccatgt actgcatgct gtttgtggca ctttatcttc aagccaggat gaagggagac
540

tgggcaagac tcttacgccc cacactgcaa tttggtcttg ttgccgtatc catttatgtg
600

ggcctttctc gagtttctga ttataaacac cactggagcg atgtgttgac tggactcatt
660

cagggagctc tggttgcaat attagttgct gtatatgtat cggatttctt caaagaaaga
720

acttctttta aagaaagaaa agaggaggac tctcatacaa ctctgcatga aacaccaaca
780

actgggaatc actatccgag caatcaccag ccttga
816

<210> 22
<211> 271
<212> PRT
<213> Homo sapiens

<400> 22

Ile Tyr Ser Leu Leu Leu Ala Gly Leu Pro Phe Ala Ile Leu Thr Ser
1 5 10 15

Arg His Thr Pro Phe Gln Arg Gly Val Phe Cys Asn Asp Glu Ser Ile
20 25 30

Lys Tyr Pro Tyr Lys Glu Asp Thr Ile Pro Tyr Ala Leu Leu Gly Gly
35 40 45

Ile Ile Ile Pro Phe Ser Ile Ile Val Ile Ile Leu Gly Glu Thr Leu
50 55 60

Ser Val Tyr Cys Asn Leu Leu His Ser Asn Ser Phe Ile Arg Asn Asn
65 70 75 80

Tyr Ile Ala Thr Ile Tyr Lys Ala Ile Gly Thr Phe Leu Phe Gly Ala
85 90 95

Ala Ala Ser Gln Ser Leu Thr Asp Ile Ala Lys Tyr Ser Ile Gly Arg
100 105 110

Leu Arg Pro His Phe Leu Asp Val Cys Asp Pro Asp Trp Ser Lys Ile
115 120 125

Asn Cys Ser Asp Gly Tyr Ile Glu Tyr Tyr Ile Cys Arg Gly Asn Ala
130 135 140

Glu Arg Val Lys Glu Gly Arg Leu Ser Phe Tyr Ser Gly His Ser Ser
145 150 155 160

Phe Ser Met Tyr Cys Met Leu Phe Val Ala Leu Tyr Leu Gln Ala Arg
165 170 175

Met Lys Gly Asp Trp Ala Arg Leu Leu Arg Pro Thr Leu Gln Phe Gly
180 185 190

Leu Val Ala Val Ser Ile Tyr Val Gly Leu Ser Arg Val Ser Asp Tyr
195 200 205

Lys His His Trp Ser Asp Val Leu Thr Gly Leu Ile Gln Gly Ala Leu
210 215 220

Val Ala Ile Leu Val Ala Val Tyr Val Ser Asp Phe Phe Lys Glu Arg
225 230 235 240

Thr Ser Phe Lys Glu Arg Lys Glu Glu Asp Ser His Thr Thr Leu His
245 250 255

Glu Thr Pro Thr Thr Gly Asn His Tyr Pro Ser Asn His Gln Pro
260 265 270

<210> 23
<211> 840
<212> DNA
<213> Murinae gen. sp.

<220>

<221> misc_feature
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<223> n is a, c, g, or t

<400> 23
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ctgactgaga agaggacgct cccgggaaac gaatgaggaa ccacctcctc ctgctgttca
120

agtacagggg cctggtgcgc aaagggaaga aaagcaaaag acgaaaatgg ctaaatttaa
180

gatccgtcca gccactgcct ctgactgcag tgacatcctg cgactgatca aggaactggc
240

taaatatgaa tacatggaag atcaagtcat tttaactgag aaagatctcc aagaggatgg
300

ctttggagaa caccccttct accactgcct ggttgcagaa gtgcctaaag agcactggac
360

ccctgaagga catagcattg ttgggttcgc catgtactat tttacctatg acccatggat
420

tggcaagttg ctgtatcttg aagacttctt cgtgatgagt gattacagag gctntggtat
480

aggatcagaa attttgaaga atctaagcca ggttgccatg aagtgtcgct gcagcagtat
540

gcacttcttg gtagcagaat ggaatgaacc atctatcaac ttctacaaaa gaagaggtgc
600

ttcggatctg tccagtgaag agggatggga ggctcttcaa gattgacaag agtacttgct
660

aaaaatggca gcagaggagt gaggcgtgcc ggtgtagaac atgacaacct ccattgtgct
720

ttagaataat tctcagcttc ccttgctttc tatcttgtgg tgtaggtgaa ataatagagc
780

gagccaccat tccaaagctt tattaccagt gacgtgttgc atgtttgaaa tcggtctggt
840

<210> 24
<211> 1052
<212> DNA
<213> Murinae gen. sp.

<400> 24
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gtcatggtgc cagcctgact gagaagagga cgctcccggg aaacgaatga ggaaccacct
120

cctcctgctg ttcaagtaca ggggcctggt gcgcaaaggg aagaaaagca aaagacgaaa
180

atggctaaat ttaagatccg tccagccact gcctctgact gcagtgacat cctgcgactg
240

atcaaggaac tggctaaata tgaatacatg gaagatcaag tcattttaac tgagaaagat
300

ctccaagagg atggctttgg agaacacccc ttctaccact gcctggttgc agaagtgcct
360

aaagagcact ggacccctga aggacatagc attgttgggt tcgccatgta ctattttacc
420

tatgacccat ggattggcaa gttgctgtat cttgaagact tcttcgtgat gagtgattac
480

agaggctttg gtataggatc agaaattttg aagaatctaa gccaggttgc catgaagtgt
540

cgctgcagca gtatgcactt cttggtagca gaatggaatg aaccatctat caacttctac
600

aaaagaagag gtgcttcgga tctgtccagt gaagagggat ggaggctctt caagattgac
660

aaagagtact tgctaaaaat ggcagcagag gagtgaggcg tgccggtgta gacaatgaca
720

acctccattg tgctttagaa taattctcag cttcccttgc tttctatctt gtgtgtagtg
780

aaataataga gcgagcaccc attccaaagc tttattacca gtgacgttgt tgcatgtttg
840

aaattcggtc tgtttaaagt ggcagtcatg tatgtggttt ggaggcagaa ttcttgaaca
900

tcttttgatg aagaacaagg tggtatgatc ttactatata agaaaaacaa aacttcattc
960

ttgtgagtca tttaaatgtg tacaatgtac acactggtac ttagagtttc tgttttgatt
1020

ctttttttttt taaataaact actctttgat tt
1052

<210> 25
<211> 171
<212> PRT
<213> Murinae gen. sp.

<400> 25

Met Ala Lys Phe Lys Ile Arg Pro Ala Thr Ala Ser Asp Cys Ser Asp
1 5 10 15

Ile Leu Arg Leu Ile Lys Glu Leu Ala Lys Tyr Glu Tyr Met Glu Asp

20 25 30

Gln Val Ile Leu Thr Glu Lys Asp Leu Gln Glu Asp Gly Phe Gly Glu
35 40 45

His Pro Phe Tyr His Cys Leu Val Ala Glu Val Pro Lys Glu His Trp
50 55 60

Thr Pro Glu Gly His Ser Ile Val Gly Phe Ala Met Tyr Tyr Phe Thr
65 70 75 80

Tyr Asp Pro Trp Ile Gly Lys Leu Leu Tyr Leu Glu Asp Phe Phe Val
85 90 95

Met Ser Asp Tyr Arg Gly Phe Gly Ile Gly Ser Glu Ile Leu Lys Asn
100 105 110

Leu Ser Gln Val Ala Met Lys Cys Arg Cys Ser Ser Met His Phe Leu
115 120 125

Val Ala Glu Trp Asn Glu Pro Ser Ile Asn Phe Tyr Lys Arg Arg Gly
130 135 140

Ala Ser Asp Leu Ser Ser Glu Glu Gly Trp Arg Leu Phe Lys Ile Asp
145 150 155 160

Lys Glu Tyr Leu Leu Lys Met Ala Ala Glu Glu
165 170

<210> 26
<211> 1111
<212> DNA
<213> Homo sapiens

<400> 26
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60

tcatggtgcc agcctgactg agaagaggac gctcccggga gacgaatgag gaaccacctc
120

ctcctactgt tcaagtacag gggcctggtc cgcaaaggga agaaaagcaa aagacgaaaa
180

tggctaaatt cgtgatccgc ccagccactg ccgccgactg cagtgacata ctgcggctga
240

tcaaggagct ggctaaatat gaatacatgg aagaacaagt aatcttaact gaaaaagatc
300

tgctagaaga tggttttgga gagcacccct tttaccactg cctggttgca gaagtgccga
360

aagagcactg gactccggaa ggtaacccct cgcccttcc agaagccaga gagaccaaca
420

ttgttggttt tgccatgtac tattttacct atgacccgtg gattggcaag ttattgtatc
480

ttgaggactt cttcgtgatg agtgattata gaggtacgat tgagctttgg cataggatca
540

gaaattctga agaatctaag ccaggttgca atgaggtgtc gctggcagca tgcacttctt
600

gggcagaatg gaatgaacca tccatcaact tctataaaag aagaggtgct tctgatctgt
660

ccagtgaaga gggttggaga ctgttcaaga tcgacaagga gtacttgcta aaaatggcaa
720

cagaggagtg aggagtgctg ctgtagatga caacctccat tctattttag aataaattcc
780

caacttctct tgctttctat gctgtttgta gtgaaataat agaatgagca cccattccaa
840

agctttatta ccagtggcgt tgttgcatgt ttgaaatgag gtctgtttaa agtggcaatc
900

tcagatgcag tttggagagt cagatctttc tccttgaata tctttcgata aacaacaagg
960

tggtgtgatc ttaatatatt tgaaaaaaac ttcattctcg tgagtcattt aaatgtgtac
1020

aatgtacaca ctggtactta gagtttctgt ttgattcttt tttaataaac tactctttga
1080

tttaattcta aaaaaaaaaa aaaaaaagac a
1111

<210> 27
<211> 190
<212> PRT
<213> Homo sapiens

<400> 27

Glu Pro Pro Pro Pro Thr Val Gln Val Gln Gly Pro Gly Pro Gln Arg
1 5 10 15

Glu Glu Lys Gln Lys Thr Lys Met Ala Lys Phe Val Ile Arg Pro Ala
20 25 30

Thr Ala Ala Asp Cys Ser Asp Ile Leu Arg Leu Ile Lys Glu Leu Ala
35 40 45

Lys Tyr Glu Tyr Met Glu Glu Gln Val Ile Leu Thr Glu Lys Asp Leu
50 55 60

Leu Glu Asp Gly Phe Gly Glu His Pro Phe Tyr His Cys Leu Val Ala
65 70 75 80

Glu Val Pro Lys Glu His Trp Thr Pro Glu Gly Asn Pro Ser Pro Phe
85 90 95

Pro Glu Ala Arg Glu Thr Asn Ile Val Gly Phe Ala Met Tyr Tyr Phe
100 105 110

Thr Tyr Asp Pro Trp Ile Gly Lys Leu Leu Tyr Leu Glu Asp Phe Phe
115 120 125

Val Met Ser Asp Tyr Arg Gly Thr Ile Glu Leu Trp His Arg Ile Arg
130 135 140

Asn Ser Glu Glu Ser Lys Pro Gly Cys Asn Glu Val Ser Leu Ala Ala
145 150 155 160

Cys Thr Ser Trp Ala Glu Trp Asn Glu Pro Ser Ile Asn Phe Tyr Lys
165 170 175

Arg Arg Gly Ala Ser Asp Leu Ser Ser Glu Glu Gly Trp Arg
180 185 190

<210> 28
<211> 745
<212> DNA
<213> Murinae gen. sp.

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120

agaggagtgt ccttcacatt tggtgcagaa gtggttgcaa aatttctcca taagcatgat
180

tcggatctta tatgtagagc ccatcaggtg gttgaagatg gctatgagtt tttcgcaaag
240

aggcagttag tcactctgtt gttctgcgag cccaactact gtggcgagtt tgacaatgca
300

ggcgccatga tgagtgtgga tgagaccctc atgtgttcct tccagatttt aaagcctgca
360

gagaaaaaga agcccaacgc cacgagacct gtcacaccac cacggggtat gatcacaaag
420

caagcaaaga aatagatgtc acttgacact gcctggttgg gacttgtaac atagcgttca
480

taaccttcct ttttaaactg tgatgtgctg gtcagcttgc ccaggtagac ctgtctgtcg
540

ggccctcctc catttgatta ctgctggcac ttgctggtta tagcagcaag ccaagcactt
600

cattctcaag agagcatttg gttctgaacc tctgttccct ttgtggacag ctctgatgat
660

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720

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745

<210> 29
<211> 2127
<212> DNA
<213> Murinae gen. sp.

<400> 29
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120

tccaggagaa cgagatccga ggactctgcc tgaagtctcg ggagatcttc ctcagtcagc
180

ctatcctttt agaacttgaa gcaccactca agatatgtgg tgacatccac gggcagtact
240

atgatttgct ccgtctgttt gaatacggtg gctttcctcc agagagcaac tatttgtttc
300

tcggggacta tgtggacagg ggcaagcagt ccctggagac aatctgcctc ttgctggcct
360

acaaaatcaa gtatccggag aacttctttc ttctcagagg gaaccacgag tgcgccagca
420

tcaataggat ctacggattt tatgatgagt gtaaaagaag atacaacatt aagctgtgga
480

aaacgttcac agactgtttt aactgcttgc cgatagcagc catcgtggac gagaagatat
540

tctgctgtca tggaggttta tcaccagatc ttcaatctat ggagcagatt cggcgaatta
600

tgagaccaac tgatgtacca gatcaaggtc ttctttgtga tcttttgtgg tctgaccccg
660

ataaagatgt cttaggctgg ggtgaaaatg acagaggagt gtccttcaca tttggtgcag
720

aagtggttgc aaaatttctc cataagcatg atttggatct tatatgtaga gcccatcagg
780

tggttgaaga tggctatgag ttttttgcaa agaggcagtt agtcactctg ttttctgcac
840

ccaactactg tggcgagttt gacaatgcag gcgccatgat gagtgtggat gagaccctca
900

tgtgttcctt ccagatttta aagcctgcag agaaaaagaa gcccaacgcc acgagacctg
960

tcacaccacc acggggtatg atcacaaagc aagcaaagaa atagatgtca cttgacactg
1020

cctggttggg acttgtaaca tagcgttcat aaccttcctt tttaaactgt gatgtgctgg
1080

tcagcttgcc caggtagacc tgtctgtcgg gccctcctcc atttgattac tgctggcact
1140

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1260

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1320

gtaaatgcct gttttcttta ggatataaag agagccttag agtgcgtgag tctctacatg
1380

taattgtcat aaatgcattc tgttgataca aaccactgtg aacaattttt tttccagttt
1440

gtttgaaagg gactgctttc cctcattgtc ttgtcatgta caaactagtg tctgcagctg
1500

tggcagcagg agtgacctgc ctgccgccag ccctgcccag actatctgaa gcacactcct
1560

tcccactgca catttaataa tgattaaagc cattcttttc aatgtctgtg attccttcct
1620

aaagccaaag tttctgttgg actgtatggc acgccctggg gatgaggtgg ccagggcatc
1680

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1800

gttcccatat agtctattca ctgagtgatc tttttacagt tggatcaggc ctgaacccgt
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1920

tttctttggc tacattcttt attctgcggt gacattgagg cttataaatc aaaaggaact
1980

aacttgccgt ccaccggttt atacagaact cacagtatct atgacttttt taaactacga
2040

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2100

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2127

<210> 30
<211> 323
<212> PRT
<213> Murinae gen. sp.

<400> 30

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20 25 30

Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg Glu Ile Phe Leu Ser
35 40 45

Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro Leu Lys Ile Cys Gly Asp
50 55 60

Ile His Gly Gln Tyr Tyr Asp Leu Leu Arg Leu Phe Glu Tyr Gly Gly
65 70 75 80

Phe Pro Pro Glu Ser Asn Tyr Leu Phe Leu Gly Asp Tyr Val Asp Arg
85 90 95

Gly Lys Gln Ser Leu Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile
100 105 110

Lys Tyr Pro Glu Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala
115 120 125

Ser Ile Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
130 135 140

Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys Leu Pro
145 150 155 160

Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His Gly Gly Leu
165 170 175

Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg Arg Ile Met Arg Pro
180 185 190

Thr Asp Val Pro Asp Gln Gly Leu Leu Cys Asp Leu Leu Trp Ser Asp
195 200 205

Pro Asp Lys Asp Val Leu Gly Trp Gly Glu Asn Asp Arg Gly Val Ser
210 215 220

Phe Thr Phe Gly Ala Glu Val Val Ala Lys Phe Leu His Lys His Asp
225 230 235 240

Leu Asp Leu Ile Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu
245 250 255

Phe Phe Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
260 265 270

Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp Glu Thr
275 280 285

Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Glu Lys Lys Lys Pro
290 295 300

Asn Ala Thr Arg Pro Val Thr Pro Pro Arg Gly Met Ile Thr Lys Gln
305 310 315 320

Ala Lys Lys

<210> 31
<211> 993
<212> DNA
<213> Homo sapiens

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120

aaatcccggg agatttttct gagccagccc attcttctgg agctggaggc acccctcaag
180

atctgcggtg acatacacgg ccagtactac gaccttctgc gactatttga gtatggcggt
240

ttccctcccg agagcaacta cctctttctg ggggactatg tggacagggg caagcagtcc
300

ttggagacca tctgcctgct gctggcctat aagatcaagt accccgagaa cttcttcctg
360

ctccgtggga accacgagtg tgccagcatc aaccgcatct atggtttcta cgatgagtgc
420

aagagacgct acaacatcaa actgtggaaa accttcactg actgcttcaa ctgcctgccc
480

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540

cagtctatgg agcagattcg gcggatcatg cggcccacag atgtgcctga ccagggcctg
600

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660

cgtggcgtct cttttacctt tggagccgag gtggtggcca agttcctcca caagcacgac
720

ttggacctca tctgccgagc acaccaggtg gtagaagacg gctacgagtt ctttgccaag
780

cggcagctgg tgacactttt ctcagctccc aactactgtg gcgagtttga caatgctggc
840

gccatgatga gtgtggacga gaccctcatg tgctctttcc agatcctcaa gcccgccgac
900

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<210> 32
<211> 330
<212> PRT
<213> Homo sapiens

<400> 32

Met Ser Asp Ser Glu Lys Leu Asn Leu Asp Ser Ile Ile Gly Arg Leu
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Leu Glu Val Gln Gly Ser Arg Pro Gly Lys Asn Val Gln Leu Thr Glu
20 25 30

Asn Glu Ile Arg Gly Leu Cys Leu Lys Ser Arg Glu Ile Phe Leu Ser
35 40 45

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Gln Pro Ile Leu Leu Glu Leu Glu Ala Pro Leu Lys Ile Cys Gly Asp
 50                  55                  60

Ile His Gly Gln Tyr Tyr Asp Leu Leu Arg Leu Phe Glu Tyr Gly Gly
65                  70                  75                  80

Phe Pro Pro Glu Ser Asn Tyr Leu Phe Leu Gly Asp Tyr Val Asp Arg
                85                  90                  95

Gly Lys Gln Ser Leu Glu Thr Ile Cys Leu Leu Leu Ala Tyr Lys Ile
            100                 105                 110

Lys Tyr Pro Glu Asn Phe Phe Leu Leu Arg Gly Asn His Glu Cys Ala
        115                 120                 125

Ser Ile Asn Arg Ile Tyr Gly Phe Tyr Asp Glu Cys Lys Arg Arg Tyr
    130                 135                 140

Asn Ile Lys Leu Trp Lys Thr Phe Thr Asp Cys Phe Asn Cys Leu Pro
145                 150                 155                 160

Ile Ala Ala Ile Val Asp Glu Lys Ile Phe Cys Cys His Gly Gly Leu
                165                 170                 175

Ser Pro Asp Leu Gln Ser Met Glu Gln Ile Arg Arg Ile Met Arg Pro
            180                 185                 190

Thr Asp Val Pro Asp Gln Gly Leu Leu Cys Asp Leu Leu Trp Ser Asp
        195                 200                 205

Pro Asp Lys Asp Val Gln Gly Trp Gly Glu Asn Asp Arg Gly Val Ser
    210                 215                 220

Phe Thr Phe Gly Ala Glu Val Val Ala Lys Phe Leu His Lys His Asp
225                 230                 235                 240

Leu Asp Leu Ile Cys Arg Ala His Gln Val Val Glu Asp Gly Tyr Glu
                245                 250                 255

Phe Phe Ala Lys Arg Gln Leu Val Thr Leu Phe Ser Ala Pro Asn Tyr
            260                 265                 270

Cys Gly Glu Phe Asp Asn Ala Gly Ala Met Met Ser Val Asp Glu Thr
        275                 280                 285
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Leu Met Cys Ser Phe Gln Ile Leu Lys Pro Ala Asp Lys Asn Lys Gly
290 295 300

Lys Tyr Gly Gln Phe Ser Gly Leu Asn Pro Gly Gly Arg Pro Ile Thr
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Pro Pro Arg Asn Ser Ala Lys Ala Lys Lys
325 330

<210> 33
<211> 747
<212> DNA
<213> Murinae gen. sp.

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120

tgcgtatttg ttgagctggg agagtagccc agtggtacag cgcccacctg gaatacttga
180

ggacctgggg ttgtctccca gcactgcaaa aggaaaattc actgttacag tcttccttgc
240

acttaaacca gctttgtcta ttgtttttt ggtttggctt tgttactttt gttgctgntt
300

atttttgttg ttgttgtttg tttgtttgag acagggtttt tttgctagcc ctgactgtcc
360

tgaaactccc tctgtagacc aggctggcct caaacttaca gagatccgcc tgcctcagcc
420

tcccaagtgc tgggaataat ggtgtggtca ccaccgccca gccttttgtc tatttttaaa
480

cttgaaagaa acaacagccc agatttcaaa aataatataa tgcacttata cctaaaaaaa
540

caaccaggag tgcccagtta ataacatttt ttaaatgtgg ggatgggaag ggcattagag
600

gagtcttcct tctattgaag attcattaaa gtatttaaga tatgcccttt cactctttat
660

ataaatccaa gatttttctt tgctgaagta tttaaaactt ttgtaccttt atatgtagat
720

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747

<210> 34
<211> 2021
<212> DNA
<213> Murinae gen. sp.

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120

agttccaagc tctctgggaa ccggaacggc agggaaagcc gagcgggcgg cctgaaggag
180

agaagcaatg gatcagaggg ggctccaagt gaaggaaggg taagtccaaa gagcagcgtt
240

cctgagactg gcctgataga ctgcagcact tcacaggccg ccagttctcc agaaccaacc
300

agcctcaagg gctccacatc tctgcctgtt cactcagctt ccagagctag gaaagagcag
360

ggtgctggca gccattccga cgcttgaaga aaactgtctc gttcccccag aagcacatgt
420

atgttacact ggagatgacc aactgatttg tcttataaag gccactgttg agctgggaga
480

gtagcccagt ggtacagcgc ccacctggaa tacttgagga cctggggttg tctcccagca
540

ctgcaaaagg aaaattcact gttacagtct tccttgcact taaaccagct ttgtctattg
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900

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960

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1200

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1680

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1740

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1860

gttttcttag atactttgat cccattggag ctctgttaaa gtttaaaatg aaaattatca
1920

tgtactgtat gggaaatgta aatactaact tttccacata tgtaaacttc agacacaaat
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2021

<210> 35
<211> 709
<212> PRT
<213> Murinae gen. sp.

<400> 35

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20 25 30

Met Lys Met Thr Tyr Asn Met Thr Phe Phe Pro Asn Leu Met Gly His
35 40 45

Tyr Asp Gln Gly Ile Ala Ala Val Glu Met Gly His Phe Leu His Leu
50 55 60

Ala Asn Leu Glu Cys Ser Pro Asn Ile Glu Met Phe Leu Cys Gln Ala
65 70 75 80

Phe Ile Pro Thr Cys Thr Glu Gln Ile His Val Val Leu Pro Cys Arg
85 90 95

Lys Leu Cys Glu Lys Ile Val Ser Asp Cys Lys Lys Leu Met Asp Thr
100 105 110

Phe Gly Ile Arg Trp Pro Glu Glu Leu Glu Cys Asn Arg Leu Pro His
115 120 125

Cys Asp Asp Thr Val Pro Val Thr Ser His Pro His Thr Glu Leu Ser
130 135 140

Gly Pro Gln Lys Lys Ser Asp Gln Val Pro Arg Asp Ile Gly Phe Trp
145 150 155 160

Cys Pro Lys His Leu Arg Thr Ser Gly Asp Gln Gly Tyr Arg Phe Leu
165 170 175

Gly Ile Glu Gln Cys Ala Pro Pro Cys Pro Asn Met Tyr Phe Lys Ser
180 185 190

Asp Glu Leu Asp Phe Ala Lys Ser Phe Ile Gly Ile Val Ser Ile Phe
195 200 205

Cys Leu Cys Ala Thr Leu Phe Thr Phe Leu Thr Phe Leu Ile Asp Val
210 215 220

Arg Arg Phe Arg Tyr Pro Glu Arg Pro Ile Ile Tyr Tyr Ser Val Cys
225 230 235 240

Tyr Ser Ile Val Ser Leu Met Tyr Phe Val Gly Phe Leu Leu Gly Asn
245 250 255

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Ser Thr Ala Cys Asn Lys Ala Asp Glu Lys Leu Glu Leu Gly Asp Thr
            260                 265                 270

Val Val Leu Gly Ser Lys Asn Lys Ala Cys Ser Val Val Phe Met Phe
        275                 280                 285

Leu Tyr Phe Phe Thr Met Ala Gly Thr Val Trp Trp Val Ile Leu Thr
    290                 295                 300

Ile Thr Trp Phe Leu Ala Ala Gly Arg Lys Trp Ser Cys Glu Ala Ile
305                 310                 315                 320

Glu Gln Lys Ala Val Trp Phe His Ala Val Ala Trp Gly Ala Pro Gly
                325                 330                 335

Phe Leu Thr Val Met Leu Leu Ala Met Asn Lys Val Glu Gly Asp Asn
            340                 345                 350

Ile Ser Gly Val Cys Phe Val Gly Leu Tyr Asp Leu Asp Ala Ser Arg
        355                 360                 365

Tyr Phe Val Leu Leu Pro Leu Cys Leu Cys Val Phe Val Gly Leu Ser
    370                 375                 380

Leu Leu Leu Ala Gly Ile Ile Ser Leu Asn His Val Arg Gln Val Ile
385                 390                 395                 400

Gln His Asp Gly Arg Asn Gln Glu Lys Leu Lys Lys Phe Met Ile Arg
                405                 410                 415

Ile Gly Val Phe Ser Gly Leu Tyr Leu Val Pro Leu Val Thr Leu Leu
            420                 425                 430

Gly Cys Tyr Val Tyr Glu Leu Val Asn Arg Ile Thr Trp Glu Met Thr
        435                 440                 445

Trp Phe Ser Asp His Cys His Gln Tyr Arg Ile Pro Cys Pro Tyr Gln
    450                 455                 460

Ala Asn Pro Lys Ala Arg Pro Glu Leu Ala Leu Phe Met Ile Lys Tyr
465                 470                 475                 480

Leu Met Thr Leu Ile Val Gly Ile Ser Ala Val Phe Trp Val Gly Ser
                485                 490                 495
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Lys Lys Thr Cys Thr Glu Trp Ala Gly Phe Phe Lys Arg Asn Arg Lys
500 505 510

Arg Asp Pro Ile Ser Glu Ser Arg Arg Val Leu Gln Glu Ser Cys Glu
515 520 525

Phe Phe Leu Lys His Asn Ser Lys Val Lys His Lys Lys Lys His Gly
530 535 540

Ala Pro Gly Pro His Arg Leu Lys Val Ile Ser Lys Ser Met Gly Thr
545 550 555 560

Ser Thr Gly Ala Thr Thr Asn His Gly Thr Ser Ala Met Ala Ile Ala
565 570 575

Asp His Asp Tyr Leu Gly Gln Glu Thr Ser Thr Glu Val His Thr Ser
580 585 590

Pro Glu Ala Ser Val Lys Glu Gly Arg Ala Asp Arg Ala Asn Thr Pro
595 600 605

Ser Ala Lys Asp Arg Asp Cys Gly Glu Ser Ala Gly Pro Ser Ser Lys
610 615 620

Leu Ser Gly Asn Arg Asn Gly Arg Glu Ser Arg Ala Gly Gly Leu Lys
625 630 635 640

Glu Arg Ser Asn Gly Ser Glu Gly Ala Pro Ser Glu Gly Arg Val Ser
645 650 655

Pro Lys Ser Ser Val Pro Glu Thr Gly Leu Ile Asp Cys Ser Thr Ser
660 665 670

Gln Ala Ala Ser Ser Pro Glu Pro Thr Ser Leu Lys Gly Ser Thr Ser
675 680 685

Leu Pro Val His Ser Ala Ser Arg Ala Arg Lys Glu Gln Gly Ala Gly
690 695 700

Ser His Ser Asp Ala
705

<210> 36
<211> 2039
<212> DNA
<213> Homo sapiens

<400> 36
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120

cattatttcc ttaaatcatg ttcgacaagt catacaacat gatggccgga accaagaaaa
180

actaaagaaa tttatgattc gaattggagt cttcagcggc ttgtatcttg tgccattagt
240

gacacttctc ggatgttacg tctatgagca agtgaacagg attacctggg agataacttg
300

ggtctctgat cattgtcgtc agtaccatat cccatgtcct tatcaggcaa aagcaaaagc
360

tcgaccagaa ttggctttat ttatgataaa atacctgatg acattaattg ttggcatctc
420

tgctgtcttc tgggttggaa gcaaaaagac atgcacagaa tgggctgggt tttttaaacg
480

aaatcgcaag agagatccaa tcagtgaaag tcgaagagta ctacaggaat catgtgagtt
540

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660

cacttctgca gtagcaatta ctagccatga ttacctagga caagaaactt tgacagaaat
720

ccaaacctca ccagaaacat caatgagaga ggtgaaagcg gacggagcta gcacccccag
780

gttaagagaa caggactgtg gtgaacctgc ctcgccagca gcatccatct ccagactctc
840

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900

aggaaggatt agtccaaaga gtgatattac tgacactggc ctggcacaga gcaacaattt
960

gcaggtcccc agttcttcag aaccaagcag cctcaaaggt tccacatctc tgcttgttca
1020

cccggtttca ggagtgagaa aagagcaggg aggtggttgt cattcagata cttgaagaac
1080

attttctctc gttactcaga agcaaatttg tgttacactg gaagtgacct atgcactgtt
1140

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1200

ctggaaaaaa tagagttcaa gaataatatg actcatttca cacaaaggtt aatgacaaca
1260

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1320

agagttagag gaatcttcct tttctattta tgaagattct actcttggta agagtatttt
1380

aagatgtact atgctatttt acttttttga tataaaatca agatatttct ttgctgaagt
1440

atttaaatct tatccttgta tctttttata catatttgaa aataagctta tatgtatttg
1500

aacttttttg aaatcctatt caagtatttt tatcatgcta ttgtgatatt ttagcacttt
1560

ggtagctttt acactgaatt tctaagaaaa ttgtaaaata gtcttctttt atactgtaaa
1620

aaaagatata ccaaaaagtc ttataatagg aatttaactt taaaaaccca cttattgata
1680

ccttaccatc taaaatgtgt gatttttata gtctcgtttt aggaatttca cagatctaaa
1740

ttatgtaact gaaataaggt gcttactcaa agagtgtcca ctattgattg tattatgctg
1800

ctcactgatc cttctgcata tttaaaataa aatgtcctaa agggttagta gacaaaatgt
1860

tagtcttttg tatattaggc caagtgcaat tgacttccct tttttaatgt ttcatgacca
1920

cccattgatt gtattataac cacttacagt tgcttatatt ttttgtttta acttttgttt
1980

tttaacattt agaatattac attttgtatt atacagtacc tttctcagac attttgtag
2039

<210> 37
<211> 706
<212> PRT
<213> Homo sapiens

<400> 37

Met Glu Met Phe Thr Phe Leu Leu Thr Cys Ile Phe Leu Pro Leu Leu
1 5 10 15

Arg Gly His Ser Leu Phe Thr Cys Glu Pro Ile Thr Val Pro Arg Cys
20 25 30

Met Lys Met Ala Tyr Asn Met Thr Phe Phe Pro Asn Leu Met Gly His
35 40 45

Tyr Asp Gln Ser Ile Ala Ala Val Glu Met Glu His Phe Leu Pro Leu
50 55 60

Ala Asn Leu Glu Cys Ser Pro Asn Ile Glu Thr Phe Leu Cys Lys Ala
65 70 75 80

Phe Val Pro Thr Cys Ile Glu Gln Ile His Val Val Pro Pro Cys Arg
85 90 95

Lys Leu Cys Glu Lys Val Tyr Ser Asp Cys Lys Lys Leu Ile Asp Thr
100 105 110

Phe Gly Ile Arg Trp Pro Glu Glu Leu Glu Cys Asp Arg Leu Gln Tyr
115 120 125

Cys Asp Glu Thr Val Pro Val Thr Phe Asp Pro His Thr Glu Phe Leu
130 135 140

Gly Pro Gln Lys Lys Thr Glu Gln Val Gln Arg Asp Ile Gly Phe Trp
145 150 155 160

Cys Pro Arg His Leu Lys Thr Ser Gly Gly Gln Gly Tyr Lys Phe Leu
165 170 175

Gly Ile Asp Gln Cys Ala Pro Pro Cys Pro Asn Met Tyr Phe Lys Ser
180 185 190

Asp Glu Leu Glu Phe Ala Lys Ser Phe Ile Gly Thr Val Ser Ile Phe
195 200 205

Cys Leu Cys Ala Thr Leu Phe Thr Phe Leu Thr Phe Leu Ile Asp Val
210 215 220

Arg Arg Phe Arg Tyr Pro Glu Arg Pro Ile Ile Tyr Tyr Ser Val Cys
225 230 235 240

Tyr Ser Ile Val Ser Leu Met Tyr Phe Ile Gly Phe Leu Leu Gly Asp
245 250 255

Ser Thr Ala Cys Asn Lys Ala Asp Glu Lys Leu Glu Leu Gly Asp Thr
260 265 270

Val Val Leu Gly Ser Gln Asn Lys Ala Cys Thr Val Leu Phe Met Leu
275 280 285

Leu Tyr Phe Phe Thr Met Ala Gly Thr Val Trp Trp Val Ile Leu Thr
290 295 300

Ile Thr Trp Phe Leu Ala Ala Gly Arg Lys Trp Ser Cys Glu Ala Ile
305 310 315 320

Glu Gln Lys Ala Val Trp Phe His Ala Val Ala Trp Gly Thr Pro Gly
325 330 335

Phe Leu Thr Val Met Leu Leu Ala Met Asn Lys Val Glu Gly Asp Asn
340 345 350

Ile Ser Gly Val Cys Phe Val Gly Leu Tyr Asp Leu Asp Ala Ser Arg
355 360 365

Tyr Phe Val Leu Leu Pro Leu Cys Leu Cys Val Phe Val Gly Leu Ser
370 375 380

Leu Leu Leu Ala Gly Ile Ile Ser Leu Asn His Val Arg Gln Val Ile
385 390 395 400

Gln His Asp Gly Arg Asn Gln Glu Lys Leu Lys Lys Phe Met Ile Arg
405 410 415

Ile Gly Val Phe Ser Gly Leu Tyr Leu Val Pro Leu Val Thr Leu Leu
420 425 430

Gly Cys Tyr Val Tyr Glu Gln Val Asn Arg Ile Thr Trp Glu Ile Thr
435 440 445

Trp Val Ser Asp His Cys Arg Gln Tyr His Ile Pro Cys Pro Tyr Gln
450 455 460

Ala Lys Ala Lys Ala Arg Pro Glu Leu Ala Leu Phe Met Ile Lys Tyr
465 470 475 480

Leu Met Thr Leu Ile Val Gly Ile Ser Ala Val Phe Trp Val Gly Ser
485 490 495

Lys Lys Thr Cys Thr Glu Trp Ala Gly Phe Phe Lys Arg Asn Arg Lys
500 505 510

Arg Asp Pro Ile Ser Glu Ser Arg Arg Val Leu Gln Glu Ser Cys Glu
515 520 525

Phe Phe Leu Lys His Asn Ser Lys Val Lys His Lys Lys Lys His Tyr

530 535 540

Lys Pro Ser Ser His Lys Leu Lys Val Ile Ser Lys Ser Met Gly Thr
545 550 555 560

Ser Thr Gly Ala Thr Ala Asn His Gly Thr Ser Ala Val Ala Ile Thr
565 570 575

Ser His Asp Tyr Leu Gly Gln Glu Thr Leu Thr Glu Ile Gln Thr Ser
580 585 590

Pro Glu Thr Ser Met Arg Glu Val Lys Ala Asp Gly Ala Ser Thr Pro
595 600 605

Arg Leu Arg Glu Gln Asp Cys Gly Glu Pro Ala Ser Pro Ala Ala Ser
610 615 620

Ile Ser Arg Leu Ser Gly Glu Gln Val Asp Gly Lys Gly Gln Ala Gly
625 630 635 640

Ser Val Ser Glu Ser Ala Arg Ser Glu Gly Arg Ile Ser Pro Lys Ser
645 650 655

Asp Ile Thr Asp Thr Gly Leu Ala Gln Ser Asn Asn Leu Gln Val Pro
660 665 670

Ser Ser Ser Glu Pro Ser Ser Leu Lys Gly Ser Thr Ser Leu Leu Val
675 680 685

His Pro Val Ser Gly Val Arg Lys Glu Gln Gly Gly Gly Cys His Ser
690 695 700

Asp Thr
705

<210> 38
<211> 773
<212> DNA
<213> Murinae gen. sp.

<400> 38
ctgaggtgct agcaccagcc tggttgtctc tggcgggcct gaagcaagca tggatcaaga
60

ggctgtgggc aacgttgtgc tcctggccct tgtcaccctc atcagcgtgg tccagaatgc
120

gttctttgcc cacaaggtgg agcatgaaag caaggcgcat aatgggagaa gcttccagag
180

gaccgggact cttgcctttg agcgggtcta cactgccaac cagaactgcg tagatgcgta
240

ccccactttc cttgtggtac tctggactgc aggactactt tgcagccaag tccctgcagc
300

cttcgccgga ctgatgtacc tgtttgtgag gcaaaaatac tttgtcggct atctgggaga
360

gagaactcag agcacccctg gctacatctt cggcaagcgg atcatcctgt tcctgttcct
420

catgtccttc gccgggatac tcaaccatta cctcatcttc ttcttcggaa gcgactttga
480

gaactacatc agaacggtaa gcacgacgat ctccccgctg cttctcatcc cctgattgct
540

ggagacagag aaggacgctc accagatcaa tagagacgca tcataacgca acgccgcgaa
600

ggcttctgct cctcttcaag ctgtagatgc tgtcaatctt gctgccctcg gggctctgtg
660

gcatccgtta actttgcttt tccgggaaga aaaatgtctt gtgctaagct ccacccctcg
720

aatgcggcgg tgggccagga tttatgtcta catccagcct atacttctcc tgg
773

<210> 39
<211> 852
<212> DNA
<213> Murinae gen. sp.

<400> 39
ggaaggctga ggtgctagca ccagcctggt tgtctctggc gggcctgaag caagcatgga
60

tcaagaggct gtgggcaacg ttgtgctcct ggcccttgtc accctcatca gcgtggtcca
120

gaatgtgttt tttgcccact atgtggagca tgaaagcaat gcgcataatg ggagaagctt
180

ccagaggacc gggactcttg cctttgagcg ggtctacact gccaaccaga actgcgtaga
240

tgcgtacccc actttccttg tggtactctg gactgcagga ctactttgca gccaagtccc
300

tgccgccttc gccggactga tgtacctgtt tgtgaggcaa aaatactttg tcggctatct
360

gggagagaga actcagagca cccctggcta catcttcggc aagcggatca tcctgttcct
420

gttcctcatg tccttcgccg ggatactcaa ccattacctc atcttcttct tcggaagcga
480

ctttgagaac tacatcagaa cggtaagcac gacgatctcc ccgctgcttc tcatcccctg
540

attgctggag acagagaagg acgctcacca gatcaataga gacgcatcat aacgcaacgc
600

cgcgaaggct tctgctcctc ttcaagctgt agatgctgtc aatcttgctg ccctcggggc
660

tctgtggcat ccgttaactt tgcttttccg ggaagaaaaa tgtcttgtgc tagctccacc
720

cctcgaatgc ggcggtggcc caggatttat tgtctacatc cagcctatac ttctcctggc
780

ttatcctgct ttctgaagat gtcttgtaat cagacacgtg ttttcctaaa ataaagggta
840

tagacaaaat tt
852

<210> 40
<211> 161
<212> PRT
<213> Murinae gen. sp.

<400> 40

Met Asp Gln Glu Ala Val Gly Asn Val Val Leu Leu Ala Leu Val Thr
1 5 10 15

Leu Ile Ser Val Val Gln Asn Val Phe Phe Ala His Tyr Val Glu His
20 25 30

Glu Ser Asn Ala His Asn Gly Arg Ser Phe Gln Arg Thr Gly Thr Leu
35 40 45

Ala Phe Glu Arg Val Tyr Thr Ala Asn Gln Asn Cys Val Asp Ala Tyr
50 55 60

Pro Thr Phe Leu Val Val Leu Trp Thr Ala Gly Leu Leu Cys Ser Gln
65 70 75 80

Val Pro Ala Ala Phe Ala Gly Leu Met Tyr Leu Phe Val Arg Gln Lys
85 90 95

Tyr Phe Val Gly Tyr Leu Gly Glu Arg Thr Gln Ser Thr Pro Gly Tyr
100 105 110

Ile Phe Gly Lys Arg Ile Ile Leu Phe Leu Phe Leu Met Ser Phe Ala
115 120 125

Gly Ile Leu Asn His Tyr Leu Ile Phe Phe Phe Gly Ser Asp Phe Glu
130 135 140

Asn Tyr Ile Arg Thr Val Ser Thr Thr Ile Ser Pro Leu Leu Leu Ile
145 150 155 160

Pro

<210> 41
<211> 873
<212> DNA
<213> Homo sapiens

<400> 41
acttcccctt cctgtacagg gcaggttgtg cagctggagg cagagcagtc ctctctgggg
60

agcctgaagc aaacatggat caagaaactg taggcaatgt tgtcctgttg gccatcgtca
120

ccctcatcag cgtggtccag aatggattct ttgcccataa agtggagcac gaaagcagga
180

cccagaatgg gaggagcttc cagaggaccg gaacacttgc ctttgagcgg gtctacactg
240

ccaaccagaa ctgtgtagat gcgtacccca ctttcctcgc tgtgctctgg tctgcggggc
300

tactttgcag ccaagttcct gctgcgtttg ctggactgat gtacttgttt gtgaggcaaa
360

agtactttgt cggttaccta ggagagagaa cgcagagcac ccctggctac atatttggga
420

aacgcatcat actcttcctg ttcctcatgt ccgttgctgg catattcaac tattacctca
480

tcttcttttt cggaagtgac tttgaaaact acataaagac gatctccacc accatctccc
540

ctctacttct cattccctaa ctctctgctg aatatggggt tggtgttctc atctaatcaa
600

tacctacaag tcatcataat tcagctcttg agagcattct gctcttcttt agatggctgt
660

aaatctattg gccatctggg cttcacagct tgagttaacc ttgcttttcc gggaacaaaa
720

tgatgtcatg tcagctccgc cccttgaaca tgaccgtggc cccaaatttg ctattcccat
780

gcattttgtt tgtttcttca cttatcctgt tctctgaaga tgttttgtga ccaggtttgt
840

gttttcttaa aataaaatgc agagacatgt ttt
873

<210> 42
<211> 161
<212> PRT
<213> Homo sapiens

<400> 42

Met Asp Gln Glu Thr Val Gly Asn Val Val Leu Leu Ala Ile Val Thr
1 5 10 15

Leu Ile Ser Val Val Gln Asn Gly Phe Phe Ala His Lys Val Glu His
20 25 30

Glu Ser Arg Thr Gln Asn Gly Arg Ser Phe Gln Arg Thr Gly Thr Leu
35 40 45

Ala Phe Glu Arg Val Tyr Thr Ala Asn Gln Asn Cys Val Asp Ala Tyr
50 55 60

Pro Thr Phe Leu Ala Val Leu Trp Ser Ala Gly Leu Leu Cys Ser Gln
65 70 75 80

Val Pro Ala Ala Phe Ala Gly Leu Met Tyr Leu Phe Val Arg Gln Lys
85 90 95

Tyr Phe Val Gly Tyr Leu Gly Glu Arg Thr Gln Ser Thr Pro Gly Tyr
100 105 110

Ile Phe Gly Lys Arg Ile Ile Leu Phe Leu Phe Leu Met Ser Val Ala
115 120 125

Gly Ile Phe Asn Tyr Tyr Leu Ile Phe Phe Phe Gly Ser Asp Phe Glu
130 135 140

Asn Tyr Ile Lys Thr Ile Ser Thr Thr Ile Ser Pro Leu Leu Leu Ile
145 150 155 160

Pro

<210> 43
<211> 803
<212> DNA
<213> Murinae gen. sp.

<400> 43

ttcagcttta tgggttggct tccttgactg cattttctgt cagttaacta aactccagac
60

tcatggattt tctcgaccag aaaatcagac tattttcctg aataatctac tagaaacttt
120

tacggaacac atttcatgtt tcctttgaag agttaagaga agaaagtatt tgtaagaaca
180

ggaaaagaaa caaatacttt gcaaataaac tggctgctgc tgtgaccaca tctgaatagc
240

aaaggcgatc gatcaagcgc tgcggacaaa aggcctcctg taagctgcac tgcctgacaa
300

tggtaagctc caatggctcc cagtgccctt atgacgactc ctttaagtac actctgtacg
360

ggtgcatgtt cagcatggtc ttcgtgcttg ggctgatatc caactgtgtt gcgatataca
420

ttttcatctg tgccctcaaa gtgagaaatg aaactacaac gtacatgatt aacctggcaa
480

tgtcagattt acttttcgtc tttactttgc catttcggat tttttacttt gcaacacgga
540

attggccatt tggagatcta ctctgtaaga tttcagtaat gctgttttac accaatatgt
600

atgggaagca ttctgttctt aacctgtatc agtgtagatc gatttctggc aattgtctac
660

ccatttaagt caaagacttt aagaaacgaa acgaaaatgc aaagaatcgt ttgcattgcc
720

tgtgtggttc acagtgatgg gaggaagtgc gctgcagttt tctttcagtc gacccactct
780

caggggaaca atactcagaa gct
803

<210> 44
<211> 1849
<212> DNA
<213> Murinae gen. sp.

<400> 44
agagacagcc catctcacaa tacagctggc aacctccgaa aggcctctcc attcagcaag
60

cgcgaacatg cttaggaatt tatctgggat cccttaaacg actgcctatc gccgtccgga
120

atcaatgtag aaatacaaag tttgagaata aaaagaagga agaagtaccc gaggacgacg
180

ggcggacgga cgcacggcga gtgtttgtga ctgaagtaaa gctggtttgg accctggcgg
240

ctgaagcaca agtttccacg cggactggtc tggtccgact tggaacagtt tttccttaca
300

ctttcagctt tatgggttgg cttccttgac tgcattttct gtcagttaac taaactccag
360

actcatggat tttctcgacc agaaaatcag actattttcc tgaataatct actagaaact
420

tttacggaac acatttcatg tttcctttga agagttaaga gaagaaagta tttgtaagaa
480

caggaaaaga aacaaatact ttgcaaataa actggctgct gctgtgacca catctgaata
540

gcaaaggcga tcgatcaagc gctgcggaca aaaggcctcc tgtaagctgc actgcctgac
600

aatggtaagc tccaatggct cccagtgccc ttatgacgac tcctttaagt acactctgta
660

cgggtgcatg ttcagcatgg tcttcgtgct tgggctgata tccaactgtg ttgcgatata
720

cattttcatc tgtgccctca aagtgagaaa tgaaactaca acgtacatga ttaacctggc
780

aatgtcagat ttacttttcg tctttacttt gccatttcgg atttttttact ttgcaacacg
840

gaattggcca tttggagatc tactctgtaa gatttcagta atgctgtttt acaccaatat
900

gtatggaagc attctgttct taacctgtat cagtgtagat cgatttctgg caattgtcta
960

cccatttaag tcaaagactt taagaacgaa acgaaatgca aagatcgttt gcattgctgt
1020

gtggttcaca gtgatgggag gaagtgcgcc tgcagttttc tttcagtcga cccactctca
1080

ggggaacaat acctcagaag cctgctttga gaactttcca gcggccacat ggaaaactta
1140

tctctccagg attgtgattt tcattgaaat agtgggcttt tttatccctc tcattttgaa
1200

cgtaacttgt tctagtatgg tgctaagaac tttaaataaa cctgttacat taagtagaag
1260

caaaatgaac aaaactaagg ttttaaaaat gatttttgtc cacttggtca tcttctgttt
1320

ctgttttgtg ccctacaaca tcaacctcat tttgtactcg ctcatgagga cacagacctt
1380

tgttaactgc tctgtggtgg cggcagtgag gaccatgtac ccgatcactc tctgcatcgc
1440

tgtttccaac tgctgctttg accctattgt ttactacttc acctcagaca caattcagaa
1500

ctcaataaaa atgaaaaact ggtcggttag aagaagtgac tccaggttct ctgaagttca
1560

gggcactgag aattttatcc aacacaacct acagacctta aaaaataaga tatttgataa
1620

tgaatctgca atataagctg cctgactaag ccactgggac tgctccgtgt tcaactgtga
1680

aaactgtgtt cttgggaact atctctccgg ctccaacaga aaatattttt aaaggaagtt
1740

tgtgtctgat gtgttaaaca ttaaaatata ttctattctt gtatgcacgc cattttactt
1800

tcttgaacca ctttaacgtg ttttttcctc attaaaaaaa aaaaactcc
1849

<210> 45
<211> 316
<212> PRT
<213> Murinae gen. sp.

<400> 45

Asp Asp Ser Phe Lys Tyr Thr Leu Tyr Gly Cys Met Phe Ser Met Val
1 5 10 15

Phe Val Leu Gly Leu Ile Ser Asn Cys Val Ala Ile Tyr Ile Phe Ile
20 25 30

Cys Ala Leu Lys Val Arg Asn Glu Thr Thr Thr Tyr Met Ile Asn Leu
35 40 45

Ala Met Ser Asp Leu Leu Phe Val Phe Thr Leu Pro Phe Arg Ile Phe
50 55 60

Tyr Phe Ala Thr Arg Asn Trp Pro Phe Gly Asp Leu Leu Cys Lys Ile
65 70 75 80

Ser Val Met Leu Phe Tyr Thr Asn Met Tyr Gly Ser Ile Leu Phe Leu
85 90 95

Thr Cys Ile Ser Val Asp Arg Phe Leu Ala Ile Val Tyr Pro Phe Lys
100 105 110

Ser Lys Thr Leu Arg Thr Lys Arg Asn Ala Lys Ile Val Cys Ile Ala
115 120 125

Val Trp Phe Thr Val Met Gly Gly Ser Ala Pro Ala Val Phe Phe Gln
130 135 140

Ser Thr His Ser Gln Gly Asn Asn Thr Ser Glu Ala Cys Phe Glu Asn
145 150 155 160

Phe Pro Ala Ala Thr Trp Lys Thr Tyr Leu Ser Arg Ile Val Ile Phe
165 170 175

Ile Glu Ile Val Gly Phe Phe Ile Pro Leu Ile Leu Asn Val Thr Cys
180 185 190

Ser Ser Met Val Leu Arg Thr Leu Asn Lys Pro Val Thr Leu Ser Arg
195 200 205

Ser Lys Met Asn Lys Thr Lys Val Leu Lys Met Ile Phe Val His Leu
210 215 220

Val Ile Phe Cys Phe Cys Phe Val Pro Tyr Asn Ile Asn Leu Ile Leu
225 230 235 240

Tyr Ser Leu Met Arg Thr Gln Thr Phe Val Asn Cys Ser Val Val Ala
245 250 255

Ala Val Arg Thr Met Tyr Pro Ile Thr Leu Cys Ile Ala Val Ser Asn
260 265 270

Cys Cys Phe Asp Pro Ile Val Tyr Tyr Phe Thr Ser Asp Thr Ile Gln
275 280 285

Asn Ser Ile Lys Met Lys Asn Trp Ser Val Arg Arg Ser Asp Ser Arg
290 295 300

Phe Ser Glu Val Gln Gly Thr Glu Asn Phe Ile Gln
305 310 315

<210> 46
<211> 1035
<212> DNA
<213> Homo sapiens

<400> 46
atggtaagcg ttaacagctc ccactgcttc tataatgact cctttaagta cactttgtat
60

gggtgcatgt tcagcatggt gtttgtgctt gggttaatat ccaattgtgt tgccatatac
120

attttcatct gcgtcctcaa agtccgaaat gaaactacaa cttacatgat taacttggca
180

atgtcagact tgctttttgt ttttacttta cccttcagga ttttttactt cacaacacgg
240

aattggccat ttggagattt actttgtaag atttctgtga tgctgtttta taccaacatg
300

tacggaagca ttctgttctt aacctgtatt agtgtagatc gatttctggc aattgtctac
360

ccatttaagt caaagactct aagaaccaaa agaaatgcaa agattgtttg cactggcgtg
420

tggttaactg tgatcggagg aagtgcaccc gccgtttttg ttcagtctac ccactctcag
480

ggtaacaatg cctcagaagc ctgctttgaa aattttccag aagccacatg gaaaacatat
540

ctctcaagga ttgtaatttt catcgaaata gtgggatttt ttattcctct aattttaaat
600

gtaacttgtt ctagtatggt gctaaaaact ttaaccaaac ctgttacatt aagtagaagc
660

aaaataaaca aaactaaggt tttaaaaatg atttttgtac atttgatcat attctgtttc
720

tgttttgttc cttacaatat caatcttatt ttatattctc ttgtgagaac acaaacattt
780

gttaattgct cagtagtggc agcagtaagg acaatgtacc caatcactct ctgtattgct
840

gtttccaact gttgttttga ccctatagtt tactacttta catcggacac aattcagaat
900

tcaataaaaa tgaaaaactg gtctgtcagg agaagtgact tcagattctc tgaagttcat
960

ggtgcagaga attttattca gcataaccta cagaccttaa aaagtaagat atttgacaat
1020

gaatctgctg cctga
1035

<210> 47
<211> 344
<212> PRT
<213> Homo sapiens

<400> 47

Met Val Ser Val Asn Ser Ser His Cys Phe Tyr Asn Asp Ser Phe Lys
1 5 10 15

Tyr Thr Leu Tyr Gly Cys Met Phe Ser Met Val Phe Val Leu Gly Leu

20 25 30

Ile Ser Asn Cys Val Ala Ile Tyr Ile Phe Ile Cys Val Leu Lys Val
35 40 45

Arg Asn Glu Thr Thr Thr Tyr Met Ile Asn Leu Ala Met Ser Asp Leu
50 55 60

Leu Phe Val Phe Thr Leu Pro Phe Arg Ile Phe Tyr Phe Thr Thr Arg
65 70 75 80

Asn Trp Pro Phe Gly Asp Leu Leu Cys Lys Ile Ser Val Met Leu Phe
85 90 95

Tyr Thr Asn Met Tyr Gly Ser Ile Leu Phe Leu Thr Cys Ile Ser Val
100 105 110

Asp Arg Phe Leu Ala Ile Val Tyr Pro Phe Lys Ser Lys Thr Leu Arg
115 120 125

Thr Lys Arg Asn Ala Lys Ile Val Cys Thr Gly Val Trp Leu Thr Val
130 135 140

Ile Gly Gly Ser Ala Pro Ala Val Phe Val Gln Ser Thr His Ser Gln
145 150 155 160

Gly Asn Asn Ala Ser Glu Ala Cys Phe Glu Asn Phe Pro Glu Ala Thr
165 170 175

Trp Lys Thr Tyr Leu Ser Arg Ile Val Ile Phe Ile Glu Ile Val Gly
180 185 190

Phe Phe Ile Pro Leu Ile Leu Asn Val Thr Cys Ser Ser Met Val Leu
195 200 205

Lys Thr Leu Thr Lys Pro Val Thr Leu Ser Arg Ser Lys Ile Asn Lys
210 215 220

Thr Lys Val Leu Lys Met Ile Phe Val His Leu Ile Ile Phe Cys Phe
225 230 235 240

Cys Phe Val Pro Tyr Asn Ile Asn Leu Ile Leu Tyr Ser Leu Val Arg
245 250 255

Thr Gln Thr Phe Val Asn Cys Ser Val Val Ala Ala Val Arg Thr Met
260 265 270

Tyr Pro Ile Thr Leu Cys Ile Ala Val Ser Asn Cys Cys Phe Asp Pro
275 280 285

Ile Val Tyr Tyr Phe Thr Ser Asp Thr Ile Gln Asn Ser Ile Lys Met
290 295 300

Lys Asn Trp Ser Val Arg Arg Ser Asp Phe Arg Phe Ser Glu Val His
305 310 315 320

Gly Ala Glu Asn Phe Ile Gln His Asn Leu Gln Thr Leu Lys Ser Lys
325 330 335

Ile Phe Asp Asn Glu Ser Ala Ala
340

<210> 48
<211> 814
<212> DNA
<213> Murinae gen. sp.

<400> 48
gagcgcgcgt aagatggcac taccattttc tgtcaacctt cggggtgcgt aatggcctct
60

ggccaggcct agcacatgta cctcacagac caactggcaa gcagccttca gggagctcga
120

tccccaaaca gccagtcacc acctctgtcc cctcttcact gttggtcgtc agactgcctg
180

agtggacagc aggctggtcg cgttgtattt tcacttcctt cctctgactg gcttgctctt
240

gtctctcagt ctttcatccc aggcagctgc ctgaggtagg tgaggaggat ggtgagccag
300

gcaggtctac aataaaggca gctctgtccg gctccttctg gctcgtgagt gtcaccggcc
360

tggaagactg agggaatggc tcccctctct cctccccgtc tttccccagt tccttcccta
420

tgttggccca tgtgcccagg gagttggaag catcagggag accctcttag tgtggggaag
480

gaagtcagag accattgaca cagtgaagag gcaggatcat gtgttggaag cctgttagca
540

ggaccaaggt gactcttggg agagactctt gtggacacag gccgtggtgg cttgtcagac
600

cttaaagggt ccaggcccac ccctgccagg atccctggtc tgctttctcc aggacacact
660

gggacactgc tgagtaatga gcagcttatt acacacaatg ggaagagggg cagagagggc
720

tgtgtcggtt gagtctcggc tgggactgaa gtttgccata agtagtggtt gtacatccag
780

gagcctggct acctgtcttt acccccttgaa ggac
814

<210> 49
<211> 1164
<212> DNA
<213> Murinae gen. sp.

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240

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300

ccaggggtca aggctgagaa tctggagctg gccatccaga aagagatcca tgactttgcc
360

caattgagag ataatgtgta ccacgtatac cacaacacag aggacctgcg cggggagccg
420

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840

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<210> 50
<211> 388
<212> PRT
<213> Murinae gen. sp.

<400> 50

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35 40 45

Arg Val Leu Gln Lys Leu Gln Thr Asp Gly Leu Lys Glu Cys Ile Ile
50 55 60

Phe Cys Val Arg Glu Glu Pro Val Val Phe Leu Arg Ala Glu Glu Asp
65 70 75 80

Phe Val Ser Tyr Thr Pro Arg Asp Lys Glu Ser Leu His Glu Asn Leu
85 90 95

Arg Asp Pro Ser Pro Gly Val Lys Ala Glu Asn Leu Glu Leu Ala Ile
100 105 110

Gln Lys Glu Ile His Asp Phe Ala Gln Leu Arg Asp Asn Val Tyr His
115 120 125

Val Tyr His Asn Thr Glu Asp Leu Arg Gly Glu Pro His Thr Val Ala
130 135 140

Ile Arg Gly Glu Asp Gly Val Cys Val Thr Glu Glu Val Phe Lys Arg
145 150 155 160

Pro Leu Phe Leu Gln Pro Thr Tyr Arg Tyr His Arg Leu Pro Leu Pro
165 170 175

Glu Gln Gly Ala Pro Leu Glu Ala Gln Phe Asp Ala Phe Val Ser Val
180 185 190

Leu Arg Glu Thr Pro Ser Leu Leu Pro Leu Arg Asp Asn His Gly Pro
195 200 205

Leu Pro Ala Leu Leu Phe Ser Cys Gln Ser Gly Val Gly Arg Thr Asn
210 215 220

Leu Gly Met Val Leu Gly Thr Leu Val Met Phe His His Ser Arg Thr
225 230 235 240

Thr Ser Gln Leu Glu Ala Ala Ser Pro Leu Ala Lys Pro Leu Pro Met
245 250 255

Glu Gln Phe Gln Val Ile Gln Gly Phe Ile Cys Lys Val Pro Gln Gly
260 265 270

Lys Lys Met Val Glu Glu Val Asp Arg Ala Ile Ser Ala Cys Ala Glu
275 280 285

Leu His Asp Leu Lys Glu Glu Val Leu Lys Asn Gln Arg Arg Leu Glu
290 295 300

Ser Phe Arg Pro Glu Ser Arg Gly Gln Glu Cys Gly Ser Gln Gln Ala
305 310 315 320

Val Gln Gln Arg Ala Leu Trp Ser Leu Glu Leu Tyr Phe Tyr Leu Leu
325 330 335

Leu Phe Asn Tyr Tyr Leu His Glu Gln Tyr Pro Leu Ala Phe Ala Leu
340 345 350

Ser Phe Ser Arg Trp Leu Cys Thr His Pro Glu Leu Tyr Arg Leu Leu
355 360 365

Val Glu Leu Asn Ser Val Gly Pro Leu Val Pro Gly Asp Leu Ile Ala
370 375 380

Lys Gly Ser Leu
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<210> 51
<211> 4303
<212> DNA
<213> Homo sapiens

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120

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180

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240

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300

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420

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480

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540

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1020

accacctccc agccagaggc tgcccccacg caggccaagc ccctgcctat ggagcagttc
1080

caggtgatcc agagctttct ccgcatggtg ccccagggaa ggaggatggt ggaagaggtg
1140

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1200

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1260

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1380

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3120

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<210> 52
<211> 861
<212> PRT
<213> Homo sapiens

<400> 52

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Asp Ser Arg His Ser Val Ser Ile His Ser Phe Gln Ser Thr Ser Leu
35 40 45

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His Asn Ser Lys Ala Lys Ser Ile Ile Pro Asn Lys Val Ala Pro Val
    50                  55                  60

Val Ile Thr Tyr Asn Cys Lys Glu Glu Phe Gln Ile His Asp Glu Leu
65                  70                  75                  80

Leu Lys Ala His Tyr Thr Leu Gly Arg Leu Ser Asp Asn Thr Pro Glu
                85                  90                  95

His Tyr Leu Val Gln Gly Arg Tyr Phe Leu Val Arg Asp Val Thr Glu
            100                 105                 110

Lys Met Asp Val Leu Gly Thr Val Gly Ser Cys Gly Ala Pro Asn Phe
        115                 120                 125

Arg Gln Val Gln Gly Gly Leu Thr Val Phe Gly Met Gly Gln Pro Ser
    130                 135                 140

Leu Ser Gly Phe Arg Arg Val Leu Gln Lys Leu Gln Lys Asp Gly His
145                 150                 155                 160

Arg Glu Cys Val Ile Phe Cys Val Arg Glu Glu Pro Val Leu Phe Leu
                165                 170                 175

Arg Ala Asp Glu Asp Phe Val Ser Tyr Thr Pro Arg Asp Lys Gln Asn
            180                 185                 190

Leu His Glu Asn Leu Gln Gly Leu Gly Pro Gly Val Arg Val Glu Ser
        195                 200                 205

Leu Glu Leu Ala Ile Arg Lys Glu Ile His Asp Phe Ala Gln Leu Ser
    210                 215                 220

Glu Asn Thr Tyr His Val Tyr His Asn Thr Glu Asp Leu Trp Gly Glu
225                 230                 235                 240

Pro His Ala Val Ala Ile His Gly Glu Asp Asp Leu His Val Thr Glu
                245                 250                 255

Glu Val Tyr Lys Arg Pro Leu Phe Leu Gln Pro Thr Tyr Arg Tyr His
            260                 265                 270

Arg Leu Pro Leu Pro Glu Gln Gly Ser Pro Leu Glu Ala Gln Leu Asp
        275                 280                 285
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Ala Phe Val Ser Val Leu Arg Glu Thr Pro Ser Leu Leu Gln Leu Arg
    290                 295                 300

Asp Ala His Gly Pro Pro Pro Ala Leu Val Phe Ser Cys Gln Met Gly
305                 310                 315                 320

Val Gly Arg Thr Asn Leu Gly Met Val Leu Gly Thr Leu Ile Leu Leu
                325                 330                 335

His Arg Ser Gly Thr Thr Ser Gln Pro Glu Ala Ala Pro Thr Gln Ala
            340                 345                 350

Lys Pro Leu Pro Met Glu Gln Phe Gln Val Ile Gln Ser Phe Leu Arg
        355                 360                 365

Met Val Pro Gln Gly Arg Arg Met Val Glu Glu Val Asp Arg Ala Ile
    370                 375                 380

Thr Ala Cys Ala Glu Leu His Asp Leu Lys Glu Val Val Leu Glu Asn
385                 390                 395                 400

Gln Lys Lys Leu Glu Gly Ile Arg Pro Glu Ser Pro Ala Gln Gly Ser
                405                 410                 415

Gly Ser Arg His Ser Val Trp Gln Arg Ala Leu Trp Ser Leu Glu Arg
            420                 425                 430

Tyr Phe Tyr Leu Ile Leu Phe Asn Tyr Tyr Leu His Glu Gln Tyr Pro
        435                 440                 445

Leu Ala Phe Ala Leu Ser Phe Ser Arg Trp Leu Cys Ala His Pro Glu
    450                 455                 460

Leu Tyr Arg Leu Pro Val Thr Leu Ser Ser Ala Gly Pro Val Ala Pro
465                 470                 475                 480

Arg Asp Leu Ile Ala Arg Gly Ser Leu Arg Glu Asp Asp Leu Val Ser
                485                 490                 495

Pro Asp Ala Leu Ser Thr Val Arg Glu Met Asp Val Ala Asn Phe Arg
            500                 505                 510

Arg Val Pro Arg Met Pro Ile Tyr Gly Thr Ala Gln Pro Ser Ala Lys
        515                 520                 525

Ala Leu Gly Ser Ile Leu Ala Tyr Leu Thr Asp Ala Lys Arg Arg Leu
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530 535 540

Arg Lys Val Val Trp Val Ser Leu Arg Glu Glu Ala Val Leu Glu Cys
545 550 555 560

Asp Gly His Thr Tyr Ser Leu Arg Trp Pro Gly Pro Pro Val Ala Pro
565 570 575

Asp Gln Leu Glu Thr Leu Glu Ala Gln Leu Lys Ala His Leu Ser Glu
580 585 590

Pro Pro Pro Gly Lys Glu Gly Pro Leu Thr Tyr Arg Phe Gln Thr Cys
595 600 605

Leu Thr Met Gln Glu Val Phe Ser Gln His Arg Arg Ala Cys Pro Gly
610 615 620

Leu Thr Tyr His Arg Ile Pro Met Pro Asp Phe Cys Ala Pro Arg Glu
625 630 635 640

Glu Asp Phe Asp Gln Leu Leu Glu Ala Leu Arg Ala Ala Leu Ser Lys
645 650 655

Asp Pro Gly Thr Gly Phe Val Phe Ser Cys Leu Ser Gly Gln Gly Arg
660 665 670

Thr Thr Thr Ala Met Val Val Ala Val Leu Ala Phe Trp His Ile Gln
675 680 685

Gly Phe Pro Glu Val Gly Glu Glu Glu Leu Val Ser Val Pro Asp Ala
690 695 700

Lys Phe Thr Lys Gly Glu Phe Gln Val Val Met Lys Val Val Gln Leu
705 710 715 720

Leu Pro Asp Gly His Arg Val Lys Lys Glu Val Asp Ala Ala Leu Asp
725 730 735

Thr Val Ser Glu Thr Met Thr Pro Met His Tyr His Leu Arg Glu Ile
740 745 750

Ile Ile Cys Thr Tyr Arg Gln Ala Lys Ala Ala Lys Glu Ala Gln Glu
755 760 765

Met Arg Arg Leu Gln Leu Arg Ser Leu Gln Tyr Leu Glu Arg Tyr Val
770 775 780

Cys Leu Ile Leu Phe Asn Ala Tyr Leu His Leu Glu Lys Ala Asp Ser
785 790 795 800

Trp Gln Arg Pro Phe Ser Thr Trp Met Gln Glu Val Ala Ser Lys Ala
805 810 815

Gly Ile Tyr Glu Ile Leu Asn Glu Leu Gly Phe Pro Glu Leu Glu Ser
820 825 830

Gly Glu Asp Gln Pro Phe Ser Arg Leu Arg Tyr Arg Trp Gln Glu Gln
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Ser Cys Ser Leu Glu Pro Ser Ala Pro Glu Asp Leu Leu
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<210> 53
<211> 736
<212> DNA
<213> Murinae gen. sp.

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120

tccgctcggg ccagacttgc taccatccca ttcgcgggga ccagctggct ctgctggggc
180

gcaggactta tcctcggccg catgagtacc tgtccccagc ggatctcccc aagaattggg
240

actggagaaa tgtgaacggt gtcaactatg ccagcgtcac caggaaccag cacatcccac
300

agtactgtgg ttcctgctgg gcccacggca gcaccagtgc catggcagac cgaatcaaca
360

tcaagaggaa aggtgcatgg ccctccatcc tgctgtccgt acagaatgtc attgactgtg
420

gcaatgctgg ctcttgtgaa gggggcaatg accttccggt gtgggagtat gcccacaagc
480

atggcatccc cgatgagacc tgcaacaact accaggcaag gaccaagact gtgacaagtt
540

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600

ctggagagtg ggtgattacg gtccctgtcc gggagggaga agatgatggc gagatctatg
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736

<210> 54
<211> 1404
<212> DNA
<213> Murinae gen. sp.

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120

cggtgcagca gctgcccctg gtgctgctga tgttgctgtt ggcgagtgcg gcacgggcca
180

gactctactt ccgctcgggc cagacttgct accatcccat tcgcggggac cagctggctc
240

tgctggggcg caggacttat cctcggccgc atgagtacct gtccccagcg gatctcccca
300

agaattggga ctggagaaat gtgaacggtg tcaactatgc cagcgtcacc aggaaccagc
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acatcccaca gtactgtggt tcctgctggg cccacggcag caccagtgcc atggcagacc
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gaatcaacat caagaggaaa ggtgcatggc cctccatcct gctgtccgta cagaatgtca
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600

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660

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720

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780

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1404

<210> 55
<211> 306
<212> PRT
<213> Murinae gen. sp.

<400> 55

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Leu Leu Leu Ala Ser Ala Ala Arg Ala Arg Leu Tyr Phe Arg Ser Gly
20 25 30

Gln Thr Cys Tyr His Pro Ile Arg Gly Asp Gln Leu Ala Leu Leu Gly
35 40 45

Arg Arg Thr Tyr Pro Arg Pro His Glu Tyr Leu Ser Pro Ala Asp Leu
50 55 60

Pro Lys Asn Trp Asp Trp Arg Asn Val Asn Gly Val Asn Tyr Ala Ser
65 70 75 80

Val Thr Arg Asn Gln His Ile Pro Gln Tyr Cys Gly Ser Cys Trp Ala
85 90 95

His Gly Ser Thr Ser Ala Met Ala Asp Arg Ile Asn Ile Lys Arg Lys
100 105 110

Gly Ala Trp Pro Ser Ile Leu Leu Ser Val Gln Asn Val Ile Asp Cys

115 120 125

Gly Asn Ala Gly Ser Cys Glu Gly Gly Asn Asp Leu Pro Val Trp Glu
130 135 140

Tyr Ala His Lys His Gly Ile Pro Asp Glu Thr Cys Asn Asn Tyr Gln
145 150 155 160

Ala Lys Asp Gln Asp Cys Asp Lys Phe Asn Gln Cys Gly Thr Cys Thr
165 170 175

Glu Phe Lys Glu Cys His Thr Ile Gln Asn Tyr Thr Leu Trp Arg Val
180 185 190

Gly Asp Tyr Gly Ser Leu Ser Gly Arg Glu Lys Met Met Ala Glu Ile
195 200 205

Tyr Ala Asn Gly Pro Ile Ser Cys Gly Ile Met Ala Thr Glu Met Met
210 215 220

Ser Asn Tyr Thr Gly Gly Ile Tyr Ala Glu His Gln Asp Gln Ala Val
225 230 235 240

Ile Asn His Ile Ile Ser Val Ala Gly Trp Gly Val Ser Asn Asp Gly
245 250 255

Ile Glu Tyr Trp Ile Val Arg Asn Ser Trp Gly Glu Pro Trp Gly Glu
260 265 270

Lys Gly Trp Met Arg Ile Val Thr Ser Thr Tyr Lys Gly Gly Thr Gly
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Asp Ser Tyr Asn Leu Ala Ile Glu Ser Ala Cys Thr Phe Gly Asp Pro
290 295 300

Ile Val
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<210> 56
<211> 1480
<212> DNA
<213> Homo sapiens

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120

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240

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Thr Tyr Pro Arg Pro His Glu Tyr Leu Ser Pro Ala Asp Leu Pro Lys
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Arg Asn Gln His Ile Pro Gln Tyr Cys Gly Ser Cys Trp Ala His Ala
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Ser Thr Ser Ala Met Ala Asp Arg Ile Asn Ile Lys Arg Lys Gly Ala
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Ala Gly Ser Cys Glu Gly Gly Asn Asp Leu Ser Val Trp Asp Tyr Ala
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His Gln His Gly Ile Pro Asp Glu Thr Cys Asn Asn Tyr Gln Ala Lys
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Asp Gln Glu Cys Asp Lys Phe Asn Gln Cys Gly Thr Cys Asn Glu Phe

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Tyr Gly Ser Leu Ser Gly Arg Glu Lys Met Met Ala Glu Ile Tyr Ala
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Asn Gly Pro Ile Ser Cys Gly Ile Met Ala Thr Glu Arg Leu Ala Asn
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Tyr Thr Gly Gly Ile Tyr Ala Glu Tyr Gln Asp Thr Thr Tyr Ile Asn
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His Val Val Ser Val Ala Gly Trp Gly Ile Ser Asp Gly Thr Glu Tyr
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Trp Ile Val Arg Asn Ser Trp Gly Glu Pro Trp Gly Glu Arg Gly Trp
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